Myocarditis During Clozapine Treatment

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The prototypical second-generation antipsychotic clozapine has been associated with various hematologic and metabolic adverse effects. Less attention has been given to clozapine's adverse cardiac effects, including myocarditis and cardiomyopathy, despite a high associated mortality rate. Here we present the case of a young man with psychosis who developed near-fatal myocarditis after the initiation of clozapine. We review the diagnosis, management, and hypothesized pathophysiology of clozapine-induced myocarditis. We urge clinicians to be vigilant for the condition and to balance the risk of myocarditis and other side effects against the many benefits of clozapine for patients with treatment-resistant symptoms of schizophrenia.

Case Presentation

Mr. A is a 27-year-old unemployed Caucasian man who lives with and is financially supported by his wife. He has a history of schizoaffective disorder, bipolar type, with one prior suicide attempt by medication overdose and two prior psychiatric hospitalizations. His index admission to our hospital followed a suicide attempt by trazodone overdose in the context of command auditory hallucinations to kill himself. This suicide attempt was preceded by several weeks of worsening depressive symptoms, paranoid ideation, and auditory hallucinations, which occurred during antipsychotic cross-titration.

Past Psychiatric History

Mr. A was raised in a working-class family, where he lived with his parents and older sister. He withdrew from high school after the 10th grade and worked at a variety of short-term jobs until 2.5 years ago, when he was no longer able to work because of his psychiatric illness. During his teenage and young adult years, he frequently used alcohol and cocaine and occasionally smoked marijuana, but he denied using these substances in the several years before his admission. He married 3 years ago and has no children. His family psychiatric history is notable for a maternal aunt and a maternal grandfather with bipolar disorder, a paternal grandfather who was institutionalized in a psychiatric hospital for unclear reasons, and several family members with substance dependence. Mr. A's medical history is significant for recurrent urinary tract infections and prostatitis. He had no history of cardiopulmonary disease before admission.

Mr. A has had depressive symptoms and paranoia since high school, and these became more prominent over the past 2 years. He reported a 1–2-week manic episode several years ago during which he "stayed up all night," overspent, and experienced increased goal-directed activity. His first psychiatric hospitalization occurred 3 years before the index admission for severe depressive symptoms. He was hospitalized again 2 years ago after a suicide attempt by an overdose of sleeping pills. After his discharge, he lived at home with his wife and attended a nearby psychiatric day program. He had monthly visits with a psychiatrist and weekly visits with a therapist and was followed by an intensive case manager. During this time, he was treated with risperidone, olanzapine, and lithium.

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History of Present Illness

According to Mr. A's outpatient psychiatrist, his mood and psychotic symptoms have responded well to this medication regimen; however, he experienced significant weight gain while taking olanzapine and diarrhea and confusion while taking lithium. Because of these adverse effects, Mr. A's psychiatric medications were discontinued, and ziprasidone was titrated to 40 mg b.i.d. 6 months before admission. This resulted in akathisia and confusion, and ziprasidone was subsequently cross-tapered to quetiapine, 800 mg/day, and divalproex sodium, 750 mg/day. Mr. A was treated with these medications for several months, with fair control of his symptoms.

One month before his admission, quetiapine was cross-tapered to aripiprazole, 5 mg/day, because of residual psychotic symptoms. Mr. A then developed a worsening of his depressed mood, anhedonia, insomnia, decreased appetite, decreased energy, feelings of worthlessness, and passive suicidal ideation. He became extremely guarded and paranoid, with the belief that his wife was "putting disgusting things in [his] food" and was "out to get [him] by rearranging [his] medication bottles so that [he] would be confused...and take the wrong medications." Mr. A also reported auditory hallucina-

tions of voices telling him, "Your wife doesn't love you," and also command auditory hallucinations to kill himself.

In this context, Mr. A decided to attempt suicide. While his wife was at work, he cut one wrist superficially and then took approximately 20 150-mg tablets of trazodone. When Mr. A's wife returned from work, she noticed that he had vomited in the toilet and questioned him about the afternoon's events. Mr. A admitted the suicide attempt, and his wife drove him to the emergency department of our hospital.

In the emergency department, a urine toxicology screen was negative, and blood alcohol, acetaminophen, and salicylate levels were zero. Significant laboratory values included a creatinine level of 1.3 mg/dl, a WBC count of 10.6×10^9/liter, and urine studies notable for the presence of leukocyte esterase and 20 WBCs per high-powered field. An ECG was within normal limits. A valproic acid level was subtherapeutic at 42.2 μg/ml. Quetiapine was restarted at 100 mg each morning and 200 mg at bedtime. Divalproex was initiated at 750 mg/day. Mr. A was admitted on a voluntary basis to our psychiatric facility.

Hospital Course

Upon arrival at the unit, Mr. A endorsed a depressed mood, suicidal ideation, and command auditory hallucinations directing him to kill himself. He also described derogatory auditory hallucinations telling him, "You're a bad person," and, "You ruin people's lives." During interviews, he was guarded and appeared internally preoccupied. Mr. A's family reported that his symptoms had been best controlled by quetiapine and divalproex in combination and that risperidone had not been effective. Quetiapine was titrated to 800 mg/day, and lamotrigine was gradually titrated to 37.5 mg/day to address Mr. A's persistent depressive symptoms.

With these medications, Mr. A's symptoms improved substantially. Although his auditory hallucinations continued, they were less intrusive, and he no longer heard commands. In addition, he reported an improved mood, and both staff and family noted a more reactive affect and better relatedness. Mr. A continued to endorse paranoia regarding his wife's intentions, and he also endorsed delusions of thought broadcasting and thought control.

Despite a promising initial response, Mr. A's condition deteriorated in the subsequent 2 weeks. He reported more intense feelings of worthlessness and guilt, and his affect appeared more depressed. He became increasingly paranoid and isolative on the unit, expressing intrusive thoughts that people were trying to poison his food. At one point, he refused to eat all hospital meals and accepted only packaged, store-bought food. He also stopped watching television because he felt that commentators were sending him personalized messages. Quetiapine was increased to 1200 mg/day without amelioration of his psychotic symptoms.

Because of Mr. A's deteriorating condition and the ineffectiveness or intolerability of previous antipsychotics, the treatment team discussed a trial of clozapine with Mr. A and his family. They agreed, and quetiapine was gradually tapered to 800 mg/day while clozapine was titrated to 200 mg b.i.d. Mr. A's WBC counts were within normal limits at baseline and 1 week after clozapine initiation. Although Mr. A experienced significant sedation during clozapine titration, he appeared better related and showed partial improvement in his paranoid ideation.

Three days after clozapine initiation, Mr. A began to complain of flu-like symptoms, including generalized body aches, nasal congestion, and "a scratchy throat." Ten days later, after an increase in his clozapine dose from a total of 300 to 400 mg/day, he was noted to have slight dysarthria, fever to 101.7°F, tachycardia to 130 bpm, and an acute mental status change. Mr. A became lethargic and disoriented. He intermittently answered questions inappropriately and was unable to follow commands. Medical and neurology consultants were called to evaluate him, and a laboratory workup was initiated. His WBC count was 9.4×10^9/liter. An ECG revealed sinus tachycardia but was otherwise unchanged from baseline. The impression of the consulting services was that Mr. A was experiencing medication-induced delirium, with an independent fever of unknown origin, most likely secondary to his recurrent urinary tract infection. The next morning, clozapine was discontinued, and considerable improvement in Mr. A's mental status resulted.

Mr. A continued to be febrile to 101°F. Blood cultures, urine studies, and a chest radiograph were unremarkable. The possibility of clozapine-induced myocarditis was considered. Serum troponin level, a highly sensitive and specific biomarker for myocardial damage, was found to be elevated at 4.9 ng/ml (<0.3 ng/ml upon admission). A repeat ECG demonstrated sinus tachycardia with T-wave inversion in lead III. A trans-thoracic echocardiogram was interpreted as normal, except for mild left ventricular hypertrophy and trace pericardial effusion. Mr. A's WBC count rose to 11.4×10^9/liter, with an increase in eosinophil percentage from 0% to 4%. He was transferred to the internal medicine service for telemetry monitoring and further treatment. The medicine team's impression was that the elevated troponin level was the result of rate-related ischemia, and myocarditis was considered unlikely.

Shortly after admission to the medicine service, Mr. A underwent a repeat trans-thoracic echocardiogram, which demonstrated a decreased ejection fraction of 45% and a segmental wall motion abnormality. Mr. A was transferred to the intensive care unit for higher-level monitoring. A review of his initial trans-thoracic echocardiogram revealed a previously overlooked inferior wall motion abnormality. Serum troponin level peaked at 38.6 ng/ml, and eosinophilia reached 13%. Because of Mr. A's compromised cardiac function and rapidly rising troponin level, the cardiology team decided to perform an emergent cardiac catheterization to rule out ischemia. This revealed normal coronary arteries, severe diffuse hypokinesis, and a markedly reduced left ventricular ejection fraction of 30%. The cardiology team's impression was clozapine-induced myocarditis. A workup for other causes of myocarditis was negative.

Mr. A returned to the intensive care unit after cardiac catheterization, where he was found to have signs of congestive heart failure by chest radiography. To address this, the cardiology team began treatment with ramipril (an angiotensin-converting enzyme inhibitor) at 2.5 mg/day, intravenous furosemide (a diuretic) at 20 mg b.i.d., and carvedilol (a beta-blocker) at 3.125 mg b.i.d. Mr. A was monitored closely with serial ECGs, telemetry, daily

troponin measurements, and frequent recordings of vital signs. Over the next week, Mr. A's serum troponin level decreased to 0.5 ng/ml, and his temperature and heart rate returned to normal. A repeat trans-thoracic echocardiogram showed a recovered ejection fraction of 55%, which is within normal limits. As Mr. A's heart failure resolved, ramipril, furosemide, and carvedilol were discontinued.

After cardiac stabilization, Mr. A was transferred back to the psychiatry service. He reported mild depressive symptoms, paranoia, incomprehensible auditory hallucinations without commands, and ideas of reference regarding the television. At the request of Mr. A and his family, treatment with quetiapine and divalproex was continued. Quetiapine was titrated to 1200 mg/day. Because Mr. A's affect continued to be depressed, the team decided to gradually titrate lamotrigine to 125 mg/day and later to substitute escitalopram, 10 mg/day, for divalproex. Haloperidol was titrated to 15 mg/day for persistent psychotic symptoms. After these changes, Mr. A's delusions decreased such that he could eat meals without significant intrusive thoughts and watch television without fear of receiving messages. Although his paranoia and hallucinations continued in an attenuated form, his insight regarding his illness improved significantly. At the time of discharge, he was well related and hopeful about the future.

During the months after his episode of acute myocarditis, Mr. A continued to experience occasional episodes of chest pain consistent with residual pericarditis that may occur during the resolution of myocarditis. Serial echocardiograms have confirmed a trace pericardial effusion but no other abnormalities. Mr. A's ventricular ejection fraction has remained normal, his serum troponin level is consistently undetectable, and an exercise stress test demonstrated no evidence of ischemia.

Discussion

As the present case illustrates, clinical suspicion for clozapine-induced myocarditis is often low. Our patient's fever, tachycardia, and leukocytosis during clozapine titration were initially attributed to a recurrent urinary tract infection. Rate-related ischemia was invoked to explain a newly elevated troponin level, and a wall motion abnormality on echocardiography was overlooked, even in the setting of known myocardial damage and ECG changes.

Many physicians may be unaware of clozapine-induced myocarditis because early studies found that, at least in its fulminant form, the condition is uncommon. Case series and data-mining studies have estimated the risk of clozapine-induced myocarditis at 0.015% to 0.188% (1–5). The true risk is likely higher, as often only a minority of adverse medication-related events are diagnosed and reported (6). Recent retrospective studies have found that as many as 66% of the patients treated with clozapine develop some findings consistent with myocarditis, although these are nonspecific (7–8).

In fact, the nonspecificity of clinical findings likely contributes to the infrequency with which myocarditis is diagnosed in clozapine-treated patients. Although fever, tachycardia, chest pain, dyspnea, flu-like symptoms, eosinophilia, elevated cardiac enzyme levels, and ECG changes may all be present in clozapine-induced myocarditis (9), no single finding is pathognomonic. Even endomyocardial biopsy, the diagnostic gold standard, has limited sensitivity and specificity, and diagnosis is usually guided by a preponderance of clinical evidence (10).

Clozapine-induced myocarditis may also be underrecognized because, in its nonfulminant form, the disorder often temporally and symptomatically resembles normal clozapine dose titration. Approximately 80% of cases of clozapine-induced myocarditis occur within 4 weeks of drug initiation, and 90% occur within 8 weeks (1, 4, 5). Many characteristics of clozapine-induced myocarditis—particularly fever, tachycardia, and fatigue—are common during clozapine titration (9). For example, fever occurs in 20% of the patients commencing treatment with clozapine and is considered a "benign, self-limited phenomenon" (11). The present case demonstrates, however, that pyrexia should not be assumed to be a benign side effect of clozapine titration. Rather, fever may be one of the heralding signs of clozapine-induced myocarditis, and cardiopulmonary symptoms need not be present early in the development of the condition.

Progression to fulminant clozapine-induced myocarditis may be rapid, with an attendant mortality rate as high as 50% (1, 4, 5). In general, prompt diagnosis, discontinuation of clozapine, and supportive treatment lead to spontaneous resolution (9). Beta-blocking agents, angiotensin-converting enzyme inhibitors, and diuretics may be helpful in the management of myocarditis, and some have shown immunomodulatory as well as hemodynamic benefit (12). The adjunctive use of corticosteroids in clozapine-induced myocarditis remains controversial (9). Rechallenge with clozapine should be relatively contraindicated because most patients, although not all, experience recurrence of myocarditis when the drug is restarted (9).

A further incentive for early diagnosis of clozapine-induced myocarditis is the potential to avert dangerous sequelae. It is possible, for example, that nonfulminant, even subclinical, clozapine-induced myocarditis may progress to dilated cardiomyopathy (9), a condition characterized by cardiac dysfunction and often symptoms of congestive heart failure. Viral myocarditis has been associated with subsequent development of cardiomyopathy, and the same may occur with clozapine-induced myocarditis. Indeed, clozapine has been associated with an elevated risk of cardiomyopathy, particularly among patients 15–44 years old (9). Cardiomyopathy is itself associated with significant morbidity and mortality, with one-half of the patients dying within 5 years of diagnosis (9).

The pathophysiology of clozapine-induced myocarditis is not definitively known. Among various early hypotheses (9), the most compelling was advanced by Killian et al. (1), who argued that clozapine-induced myocarditis likely results from a type I Ig E-mediated acute hypersensitivity reaction. The time of onset of clozapine-induced myocarditis and the peripheral eosinophilia and eosinophilic myocardial infiltrates commonly seen in the disorder all support the hypothesis of Killian et al. A number of other

drugs, including the sulfonamides, hydrochlorothiazide, the penicillins, and methyldopa, have also been associated with hypersensitivity or allergic myocarditis.

Other possible mechanisms of clozapine-induced myocarditis involve clozapine-induced cytokine release and hypercatecholaminemia. Clozapine stimulates in vivo release of tumor necrosis factor-alpha and various interleukins (13). These proinflammatory cytokines have been found to mediate autoimmune myocarditis (12) and may act similarly in clozapine-induced myocarditis. Clozapine is also known to increase serum catecholamine levels (14). Cocaine shares this effect and has been shown to exacerbate viral myocarditis (15), suggesting a role for catecholamines in the development of the disorder. Of interest, high norepinephrine levels have also been implicated in the therapeutic efficacy of clozapine (14). Whether the pathophysiology of clozapine-induced myocarditis and clozapine's mechanism of therapeutic action share a common biological basis remains to be determined. Similarly, it is unknown whether clozapine-induced myocarditis is related to clozapine-induced agranulocytosis.

Because clozapine-induced myocarditis is sometimes subtle in its presentation, the consequences can be grave, and early diagnosis and management usually lead to rapid recovery, it would be of great benefit to have an effective screening assay for this condition. At least one center in Australia monitors clozapine-treated patients with serial measurements of serum troponin level (16). At present, the clinical utility of such screening is unknown.

Until an effective screening assay for clozapine-induced myocarditis is developed, we recommend that clinicians maintain a high degree of suspicion for myocarditis in their clozapine-treated patients, especially during the 2 months after drug initiation. We recommend an ECG and serum troponin or creatine kinase-MB measurement for patients who develop new evidence of cardiovascular disease, such as tachycardia, chest pain, or dyspnea, while taking clozapine. These tests should also be considered for clozapine-treated patients with fever, flu-like symptoms, or eosinophilia. If significant changes from baseline are detected, a cardiology consultation should be strongly considered.

The current case underscores the importance of aggressively diagnosing and managing clozapine-induced myocarditis. Other clozapine-associated effects, including obesity, diabetes mellitus, hypertension, and hyperlipidemia, also contribute to cardiovascular disease, and there is some evidence that these disorders may increase mortality rates in clozapine-treated patients (17). It is unclear to what degree clozapine's deleterious cardiovascular effects offset its many salubrious properties. For example, second-generation antipsychotics, especially clozapine, likely reduce smoking, alcohol abuse, and possibly other substance abuse (9). This should result in a long-term, relative cardioprotective effect for the large majority of patients with schizophrenia who use substances that increase the risk of cardiovascular disease. Furthermore, an analysis of more than 67,000 patients found that overall mortality was decreased in current, compared to past, users of clozapine, primarily as a result of an approximate sixfold decline in suicide rate (18). The randomized, controlled International Suicide Prevention Trial (InterSePT) confirmed this benefit by finding a significant reduction in suicidal behaviors in patients treated with clozapine compared to olanzapine (19).

In deciding whether to initiate treatment with clozapine, clinicians must weigh the relative risks and benefits associated with the drug, including its distinction as the most effective medication for refractory schizophrenia (20). Once treatment with clozapine is begun, vigilance should be maintained for the development of clozapine-induced myocarditis, which may initially resemble the clinical features of normal clozapine titration and, in some cases, progress rapidly to acute heart failure.

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