



## CASE REPORT

# A case of cardiac arrest and cardiomyopathy associated with clozapine use

Rukiye Tekdemir<sup>1</sup>, Memduha Aydin<sup>2</sup>

<sup>1</sup>Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Psychiatry, Ankara - Turkey

<sup>2</sup>Selcuk University Faculty of Medicine, Department of Psychiatry, Konya - Turkey

### ABSTRACT

Clozapine is an atypical antipsychotic with proven efficacy in treatment-resistant schizophrenia. However, some possible side effects of clozapine limit its use. Cardiomyopathy is a rare, but potentially fatal, side effect. Presently described is the diagnosis and treatment of a case of cardiomyopathy associated with clozapine use. The patient was 40 years old with a 17-year history of schizophrenia. Cardiomyopathy was diagnosed 15 months after the initiation of clozapine treatment. The presence of dilated cardiomyopathy and pleural effusion was confirmed with echocardiography. Cardiopulmonary arrest led to treatment in the intensive care unit. After discharge, amisulpride treatment was introduced. It is of great importance that these cardiovascular symptoms are not overlooked in the course of clozapine treatment. Early diagnosis and treatment play a crucial role, and complaints such as fever, shortness of breath, palpitations, and fatigue must be taken into account in patients receiving clozapine. No relapse of psychotic symptoms was observed during a 7-month follow-up period, but a fraction of the cardiac symptoms persisted.

**Keywords:** Adverse effects, cardiomyopathy, clozapine, schizophrenia

### INTRODUCTION

Antipsychotics are the most important pharmacological agents used in the management of schizophrenia (1). However, despite new-generation antipsychotic drugs, not all patients with schizophrenia respond well to medication. At least 30% of patients with schizophrenia are treatment-resistant (2). It has been reported that some 40% attempt suicide during their lifetime (3) and 5% die by suicide (4). Clozapine therapy has demonstrated effectiveness in reducing the risk of suicidal behavior, and clozapine is currently the only antipsychotic that has been approved by the US Food

and Drug Administration for patients with treatment-resistant schizophrenia (2). Clozapine is used in 2% to 10% of patients with schizophrenia in Turkey (5).

Although clozapine has important benefits, it should be taken into account that clozapine can have potentially serious side effects. In addition to agranulocytosis and neutropenia, cardiac side effects are also important points of concern that could lead to morbidity or mortality. Absolute neutrophil count monitoring is required with clozapine use (6). Absolute neutrophil count monitoring increases the hematological safety of clozapine, but there are no mandatory control procedures for cardiac side effects.

**How to cite this article:** Tekdemir R, Aydin M. A case of cardiac arrest and cardiomyopathy associated with clozapine use. *Dusunen Adam The Journal of Psychiatry and Neurological Sciences* 2021;34:309-312.

**Correspondence:** Rukiye Tekdemir, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Psychiatry, Ankara - Turkey

**E-mail:** dr.rtekdemir@gmail.com

**Received:** November 03, 2020; **Revised:** November 20, 2020; **Accepted:** September 07, 2021

There have been frequent reports of cardiovascular complications associated with clozapine use (6). Myocarditis and cardiomyopathy are possibly severe and life-threatening examples. Tachycardia, arrhythmia, and hypotension are other potential cardiovascular side effects associated with clozapine use. Moreover, clozapine has been linked to pulmonary embolism, QTc prolongation, and sudden cardiac death, in addition to metabolic syndrome, which increases the risk of cardiovascular disease (6).

Clozapine-induced cardiomyopathy usually involves left ventricular dilatation. However, it can be accompanied by hypertrophy or hypertrophy with dilatation. While dilated cardiomyopathy leads to a reduced left ventricular ejection fraction (LVEF), hypertrophic cardiomyopathy leads to increased wall thickness despite a preserved LVEF. An LVEF of 50% is generally considered the threshold value for dilated cardiomyopathy, but dilated cardiomyopathy may be asymptomatic until it is severe (7). There are a limited number of case reports on this topic in the literature, but to the best of our knowledge, there is no study of the incidence of clozapine-induced cardiomyopathy. This case report describes the diagnosis and treatment of a man with schizophrenia who developed dilated cardiomyopathy after 15 months of clozapine treatment.

## CASE

A consult was requested for a 40-year-old, unmarried male patient with schizophrenia to regulate psychiatric treatment. At the time, he was unconscious and on a mechanical ventilator in the intensive care unit. According to the information provided by his relatives and treatment documents, the patient's psychiatric problems had begun 17 years earlier. An episode of aggressive behavior with visual and auditory hallucinations led his family to bring him to the hospital for psychiatric treatment. He was hospitalized for 1 month with a diagnosis of schizophrenia. He partially benefited from the treatment, but after discharge, the patient refused drug treatment and had not received any subsequent treatment for 15 years. During this period, the behavioral problems continued, and his functionality did not improve to the level of before the onset of the disorder.

After a 15-year period of treatment refusal, the second psychiatric admission had taken place 2 years earlier at another hospital, with the request of relatives that he be admitted to long-term care. A psychiatric examination that revealed psychotic symptoms and increased aggression led to hospitalization. Risperidone treatment

at 1 mg/day was applied and increased gradually, as well as a 50-mg risperidone long-acting injection, but there was no remission. Haloperidol was added to his therapy, and when no response was observed to haloperidol 20 mg/day after 2 weeks, his antipsychotic treatment was changed to clozapine with the diagnosis of treatment-resistant schizophrenia. Clozapine treatment was started at 25 mg/day and was titrated to 400 mg/day in 75 days. The clozapine dose was increased to 600 mg/day 2 months after discharge. Treatment with clozapine led to improvement in the positive psychotic symptoms, but the negative symptoms persisted. The patient attended the outpatient control visits regularly as well as activities at the community mental health center 2 days a week. He complained of a cough, shortness of breath, and sweating, but these complaints were attributed to heavy smoking (30 cigarettes/day).

In the 15th month of clozapine treatment, he was admitted to the emergency department of the same hospital with complaints of shortness of breath, cough, sudden irritability, aggression, and difficulty sleeping, and a psychiatric consultation was requested. Laboratory analysis results revealed a white blood cell count of 13.3 K/uL, a neutrophil count of 11.8 K/uL, an eosinophil count of 0.0 K/uL, a C-reactive protein (CRP) level of 102 mg/L, a troponin level of 0.07 pg/mL, ECG and a creatine kinase-MB level of 14 pg/mL. Treatment for dilated cardiomyopathy and pleural effusion was initiated based on pulmonary congestion observed in an echocardiography (echo) examination. Abnormalities were also present on electrocardiography (ECG) and chest radiography results. Based on the evaluations and interventions performed in the emergency department, the patient was referred to the psychiatric clinic. The clozapine dose was reduced to 200 mg/day and the patient was discharged.

After 1 week, the patient was brought to the emergency service of our hospital due to syncope and was hospitalized in the intensive care unit due to cardiopulmonary arrest. We evaluated the patient for the first time while he was in intensive care. He was hospitalized in the intensive care unit for 10 days. Mechanical ventilation was provided for 5 days and clozapine treatment was discontinued. He was diagnosed with clozapine-induced, dilated cardiomyopathy based on echo and physical examination findings. An ejection fraction of 30% prompted treatment with acetylsalicylic acid 100 mg/day, carvedilol 25 mg/day, spironolactone 25 mg/day, furosemide 12 mg/day, ramipril 5 mg/day, and hydrochlorothiazide 25 mg/day to treat heart failure.

It would appear that the previous treatment with haloperidol and risperidone was insufficient; they were not used at the maximum dose or for a long enough period. The patient was diagnosed with treatment-resistant schizophrenia and it was accepted that he would not benefit from risperidone and haloperidol treatment. The patient's brother, who had also been diagnosed with schizophrenia, had benefited from amisulpride therapy. Amisulpride was preferred in this case because of the good results in a first-degree relative. All antipsychotics, may have cardiovascular side effects, though it is most commonly seen in association with clozapine use (8). After discharge, amisulpride treatment was initiated to treat the psychotic symptoms and was increased to 800 mg/day in follow-up appointments. No positive psychotic symptoms were seen during a 7-month follow-up period, but cardiogenic problems of shortness of breath and high blood pressure did not improve and the patient was often hospitalized for pulmonary edema.

## DISCUSSION

This case is considered to be an example of clozapine-induced dilated cardiomyopathy based on the fact that he had no disease other than schizophrenia and had received no medication other than clozapine. He had no history of cardiovascular disease and there was no abnormality observed in routine blood test results or other medical examinations performed upon the hospitalization 15 months earlier. Although he was a heavy smoker, the patient did not use alcohol or other substances that might have contributed to the condition. His cardiogenic complaints began after clozapine treatment. His brother and his uncle were both in treatment for schizophrenia, and there was no family history of cardiovascular disease. The results of an adverse drug reaction (ADR) evaluation test indicated that the development of an ADR due to clozapine was probable (9).

Clozapine can cause fatal cardiogenic side effects, such as myocarditis and cardiomyopathy. While myocarditis is pathological myocardial inflammation, cardiomyopathy is chronic myocardial contractile dysfunction, and its pathogenesis is not yet entirely clear (10). Unrecognized or untreated myocarditis can transform into cardiomyopathy in clozapine users. Therefore, the recognition of myocarditis is important. However, this is not the only issue in the pathophysiology of cardiomyopathy. The most supported hypothesis in the literature is a immunoglobulin E-mediated

hypersensitivity reaction due to clozapine. The basis of this hypothesis is the cardiotoxic effect of clozapine and peripheral eosinophilia seen in biopsies and an increase in the number of eosinophils in myocardial tissue. Another important hypothesis is that clozapine increases the levels of catecholamine and noradrenaline. The presence of excess catecholamine discharge in Takotsubo cardiomyopathy, a left ventricular dysfunction, has been cited as evidence. Continuous tachycardia is a known cause of cardiomyopathy and is not uncommon with long-term clozapine use. A reduction in heart rate variability, another possible effect of clozapine, may also predispose an individual to cardiomyopathy. A low selenium level and increased cytokine level are other accepted causes.

Studies have reported that myocarditis can occur during the first month of clozapine use. It most commonly leads to fever, tachycardia, fatigue, dyspnea, and chest pain. However, tachycardia, eosinophilia, and fever can be common in the early stages of clozapine treatment and this should not be confused with myocarditis (10). Therefore, other necessary examinations should be performed carefully for a thorough differential diagnosis. Clozapine-induced cardiomyopathy is usually reported at about 9 months after treatment but can also occur at any time (7). One meta-analysis reported that clozapine-induced cardiomyopathy occurred at a mean of 14.4 months after treatment (11). Other studies have reported clozapine-induced cardiomyopathy at 3 weeks after treatment initiation (12) and at 4 years after treatment (13). Cardiomyopathy was diagnosed at 15 months after the start of clozapine treatment in our case.

Patients with cardiomyopathy may be completely asymptomatic, or may sometimes manifest signs and symptoms of heart failure. While cardiovascular symptoms, especially in the early stages of the disease can be overlooked, patients may present with decompensated heart failure (11). Therefore, it should be kept in mind that signs and symptoms of cardiomyopathy can vary. Symptoms such as palpitations, shortness of breath, cough, and fatigue should be closely examined (11). In our case, precursor symptoms of shortness of breath, cough, and fatigue that started after the use of clozapine were thought to be due to smoking at his earlier follow-up appointments. The diagnosis of cardiomyopathy was made after cardiopulmonary arrest.

Leukocytosis, and an elevated erythrocyte sedimentation rate and CRP value are nonspecific changes frequently observed in patients with

myocarditis. Creatine kinase and troponin are cardiac markers that should be assessed in patients with suspected myocarditis (10). Recent articles have also emphasized the importance of CRP and troponin monitoring in the early diagnosis of clozapine-induced myocarditis (10). An elevated B-type natriuretic protein level is valuable in the diagnosis of cardiomyopathy (4,6).

Monitoring an elevated eosinophil count is also recommended, but it is considered insufficient for early diagnosis, as it may only reach a level of significance once it has progressed to cardiomyopathy (10). It has also been reported that a zero eosinophil level may be a predictor of clozapine-induced late-onset agranulocytosis and that clozapine-induced eosinopenia is associated with high serum drug levels (14,15).

A chest X-ray may show pulmonary congestion and cardiomegaly. Although an ECG is usually abnormal, there is no particular associated finding. The diagnosis is confirmed with a demonstration of left ventricular dysfunction and sometimes hypertrophy on echo or another technique of evaluating cardiac function (4,6,10). In our case, both laboratory and ECG/echo findings were consistent with those reported in the literature.

The risk factors for clozapine-induced myocarditis and cardiomyopathy include genetic predisposition, advanced age, high dose and rapid dose titration, concomitant use of sodium valproate and selective serotonin reuptake inhibitors, metabolic syndrome, obesity, smoking and significant alcohol consumption (6,7). However, it should be kept in mind that clozapine-induced cardiomyopathy may be observed in patients without significant risk factors.

Clozapine-induced cardiomyopathy is an irreversible condition that can result in death. Therefore, it is vitally important that complaints such as fever, shortness of breath, palpitations, and fatigue be considered carefully in patients treated with clozapine and that the necessary examinations are performed in the early period.

Contribution Categories		Author Initials
Category 1	Concept/Design	R.T., M.A.
	Literature review	R.T., M.A.
	Data analysis/Interpretation	R.T., M.A.
	Case follow-up (if applicable)	R.T., M.A.
Category 2	Drafting manuscript	R.T., M.A.
	Critical revision of manuscript	R.T., M.A.
Category 3	Final approval and accountability	R.T., M.A.
Other	Technical or material support	R.T., M.A.
	Supervision	R.T., M.A.

**Informed Consent:** Written consent was obtained from the patient.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors have not stated any conflict of interest.

**Financial Disclosure:** The authors have not received any financial support for this study.

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