CASE REPORT

Clozapine re-exposure after dilated cardiomyopathy

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SUMMARY

A 63-year-old woman with diabetes type II and a history of breast cancer was treated with clozapine for her refractory schizophrenia. She developed a dilated cardiomyopathy with an ejection fraction of 25%, a life-threatening event. The cause of heart failure could be multifactorial, with clozapine, family history, chemotherapy, diabetes type II and/or lithium as possible contributing risk factors. Clozapine was discontinued and the patient was referred to a hospice. Two weeks later, her heart failure slowly improved. Subsequently, she became extremely psychotic with a severe decline in quality of life. Therefore, it was decided to restart clozapine under cardiac monitoring. The patient's psychotic symptoms improved and her heart failure status remained stable for more than a year. Thereafter, a small deterioration was seen in cardiac function. In this case, re-exposure to clozapine was successful for at least 2 years.

BACKGROUND

Combining clozapine with chemotherapy may lead to a higher risk of (lethal) agranulocytosis.[1] However, clozapine discontinuation may lead to exacerbation of psychotic symptoms. In clinical practice, it is therefore difficult to decide whether to continue clozapine during chemotherapy, especially because clozapine is prescribed for the treatment of refractory patients with schizophrenia.

Use of clozapine is limited by potentially life-threatening adverse effects, including agranulocytosis, myocarditis and cardiomyopathy.[2–4] The age-adjusted and sex-adjusted prevalence for dilated cardiomyopathies has been estimated to be 36.5 cases per 100 000 in the general population in the USA.[5] Survival in patients with dilated cardiomyopathy is poor. It is an often fatal cause of heart failure characterised by ventricular dilatation and impaired systolic function.[6] The ejection fraction is the most powerful predictor of mortality.[7] When a patient develops a potentially life-threatening event, such as dilated cardiomyopathy with a low (markedly impaired) ejection fraction (eg, <25%), a clinical dilemma may arise whether to continue or discontinue clozapine. We present a case of clozapine re-exposure after dilated cardiomyopathy possibly related to chemotherapy, genetic heritage, diabetes type II, clozapine and/or lithium use.

CASE PRESENTATION

A 63-year-old woman has resided in long-term psychiatric care on a voluntary basis since 1988. She was treated for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-diagnosed schizophrenia with poor therapeutic results on positive symptoms from medication. She had no history of alcohol abuse, ceased smoking at least 8 years ago and was diagnosed with diabetes type II more than 10 years ago. The refractory schizophrenia has been treated with clozapine 650 mg/day and lithium 800 mg/day for over 10 years with plasma levels within the therapeutic range. Flupentixol 20 mg/day was added in 2012. Her blood counts were within the normal range for at least 3 years. In early 2014, she was successfully treated for T1N1 breast cancer by surgery together with three cycles of FEC (5-fluorouracil, epirubicin and cyclophosphamide) and three cycles of docetaxel followed by tamoxifen. During chemotherapy, she remained treated with clozapine, flupentixol and lithium under careful monitoring of the blood counts and clozapine and lithium levels. A toxic clozapine serum level of 1177 μg/L (reference range 350–600 μg/L) was found on one occasion during chemotherapy, which resolved after dose reduction of clozapine to 400 mg/day. After the second cycle, her neutrophil count declined to 1.7×10^9/L and total leucocyte to 1.5×10^9/L, which resolved after treatment with granulocyte colony-stimulating factor injections. In June 2014, she was treated with clozapine 700 mg/day, flupentixol 25 mg/day and lithium 800 mg/day (day 0).

INVESTIGATIONS

In September 2014 (day 83 post chemotherapy), she was referred to a cardiologist with shortness of breath, cough, fluid oedema in both ankles and polyuria. She had experienced these complaints for a few days and had no prior history of these symptoms. Her blood pressure was 109/65 mm Hg, pulse 92 bpm, temperature 36.8°C. The ECG showed a sinus rhythm of 92 bpm and normal conduction times, negative T waves in the inferior leads and V6 and signs of left atrial enlargement (figure 1). The chest X-ray showed a significantly enlarged heart with a cardiothoracic ratio of 19:31: Kerley B lines were visible (figure 2). An echocardiogram showed a dilated left ventricle with a poor left ventricle systolic function (left ventricular end-diastolic dimension (LVEDD) 65 mm and ejection fraction 25%) (figure 3). Laboratory values of N-terminal brain natriuretic peptide (NT-proBNP) on day 83 and day 97 were 15 871 pg/mL and 6289 pg/mL (normal <400 pg/mL), respectively. Based on her symptoms, the heart failure was characterised as

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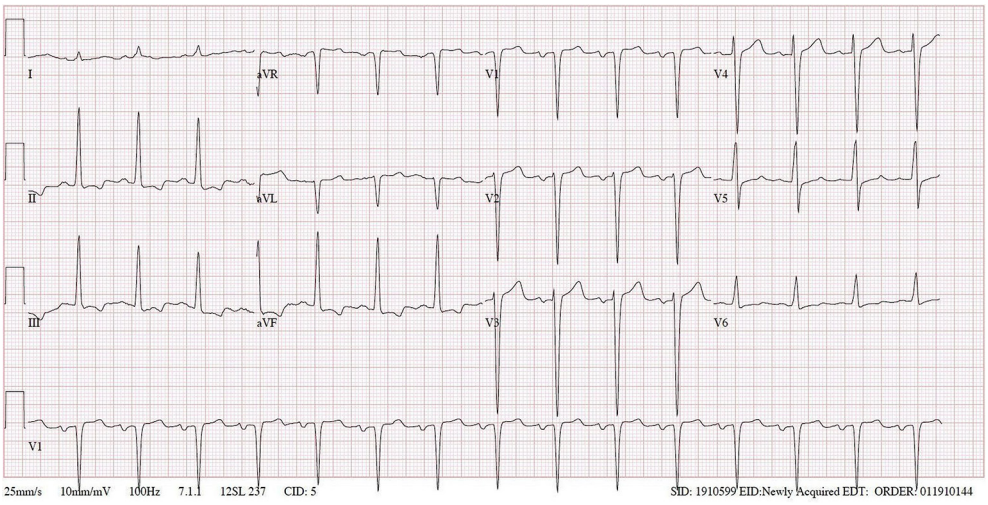

Figure 1 ECG at investigation following first cardiac symptoms.

New York Heart Association (NYHA) class IV. No abnormalities were seen on a coronary angiogram. Due to her mental state, it was not possible to obtain an MRI. Her life expectancy was estimated at between 6 months and 1 year.

DIFFERENTIAL DIAGNOSIS

It was hypothesised that her dilated cardiomyopathy could have developed due to a combination of genetic factors, chemotherapy, diabetes type II, clozapine and/or lithium. Genetic factors could have contributed to the development of the cardiomyopathy[8 9] since the patient's brother died of cardiomyopathy at the age of 56 years. Furthermore, cardiomyopathies were diagnosed for a cousin at the age of 49 years and another cousin. Several more common cardiovascular diseases were present in the family such as myocardial infarction in later life.

Anthracyclines (eg, epirubicin) have a dose-dependent and cumulative association with dilated cardiomyopathy as an adverse drug reaction.[10] The chemotherapy had been completed 3 months before diagnosis of the dilated cardiomyopathy. However, the risk of cardiotoxicity increases with time after chemotherapy.[11] Other cases have been published on cardiomyopathy following chemotherapy with fluorouracil, epirubicin, and cyclophosphamide in patients with familial cardiomyopathy.[12 13] Diabetes type II is a known risk factor for dilated cardiomyopathy and could have contributed in this case.[8]

Several studies report a higher incidence for the development of cardiomyopathy during treatment with clozapine.[3 14] In literature reports, cardiomyopathy was diagnosed between 3 weeks and 4 years after initiation of clozapine.[14] She had been using clozapine for over 10 years. Clozapine-induced cardiomyopathy seems not to be dose dependent.[14] Fewer cases have been reported on cardiomyopathy or myocarditis during lithium use compared with clozapine.[15]

TREATMENT

At day 97, clozapine was discontinued and the heart failure was treated with fluid restriction, low sodium diet, metoprolol, furosemide, spironolactone and lisinopril as recommended in the guideline of the European Society of Cardiology. An implantable cardioverter defibrillator is recommended as a treatment option in the guideline but was considered to be undesirable because of her psychiatric condition. She subsequently deteriorated and was bedridden, extremely somnolent, lacking concentration and required total care by nurses for activities of daily living. She

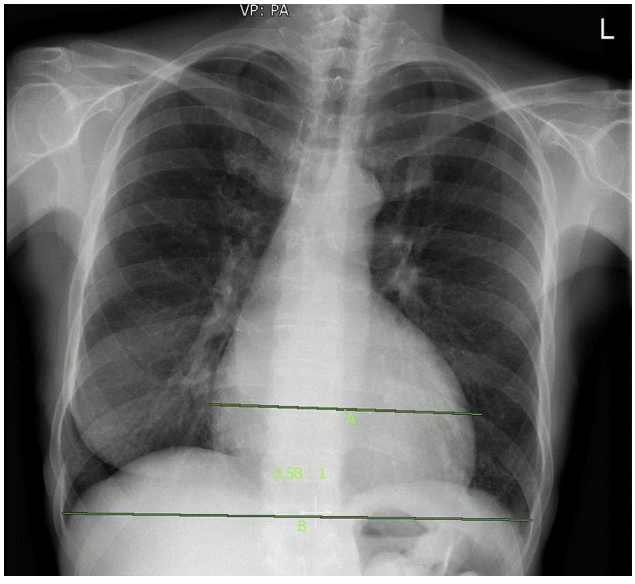

Figure 2 Chest X-ray at investigation following first cardiac symptoms with visible Kerley B lines.

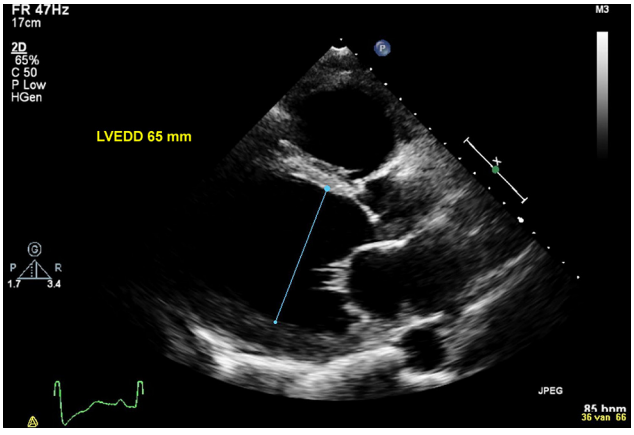

Figure 3 Echocardiogram with dilated left ventricle at investigation following first cardiac symptoms. LVEDD, left ventricular end-diastolic dimension.

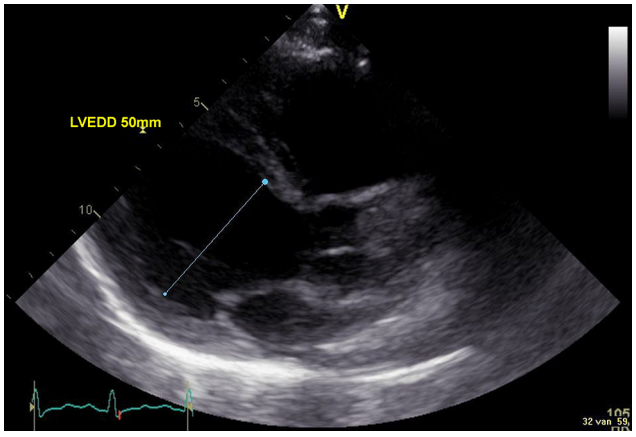

Figure 4 Echocardiogram with an improved heart function 1 year after re-initiation of clozapine. LVEDD, left ventricular end-diastolic dimension.

was transferred from the psychiatric institution to a hospice for palliative care (day 138). She was treated with olanzapine 30 mg/day and flupentixol 20 mg/day; lithium was discontinued. Her life expectancy was estimated at less than 3 months. Two weeks later, her heart failure slowly improved in the hospice (day 154). Her heart failure was thought to be improved by the medical treatment of her heart failure and/or removal of clozapine as risk factor.

After a month in the hospice (day 172), she was readmitted to the psychiatric institution with florid psychotic symptoms, sleeping only for 3 to 4 hours per night. Her actions were influenced by strange beliefs, singing songs, screaming and grabbing or throwing all objects close to her. She needed assistance with all activities of daily living and her behaviour was extremely disinhibited. Eating without close monitoring was difficult, posing a risk of choking. When she was awake, she needed two to one care.

OUTCOME AND FOLLOW-UP

Due to her severe decompensated psychosis, clozapine was re-initiated on day 210 in agreement with a cardiologist and her family. Clozapine was restarted at 12.5 mg twice a day and was gradually increased to 400 mg/day (day 250). Clinical recovery was seen at a clozapine level of 280 μg/L. Delusions with anxiety symptoms were partly unresolved; therefore, lorazepam was added and clozapine was slowly increased to a maximum of 650 mg/day (day 496). Flupentixol was decreased to 15 mg/day due to akathisia. To assess the risks of the initiation of clozapine, the psychiatrist measured her BNP value (normal, <100 pg/mL) every 2 weeks. After a year (day 598 post chemotherapy), her heart function was improved as can be seen on the echocardiogram (figure 4). Her left ventricle had become smaller in size with an LVEDD of 50 mm. Laboratory values of BNP remained low and stable during the first year of re-exposure of clozapine. Thereafter, her BNP values slowly increased (figure 5). The dosage of lorazepam was decreased. Until now, 2 years after the re-exposure, she is still successfully treated with clozapine.

DISCUSSION

To prevent harm, adequate monitoring of patients receiving cancer treatment is important. Patients with a high risk of developing adverse cardiac effects need to be identified before start of treatment. When these patients are monitored intensively, possible adverse cardiac effects can be detected early. Monitoring consists of cardiac imaging (echocardiography) and measurement of biomarkers such as NT-proBNP, troponin-I and BNP before, during and after treatment. Early detection is key to timely and adequate treatment for patients developing cardiac dysfunction.[16]

In this case, the cause of heart failure may be multifactorial, with family history, chemotherapy, diabetes type II, clozapine and/or lithium as possible contributing risk factors. Therefore, it was a difficult decision whether to continue or discontinue clozapine therapy. To our knowledge, there are only two cases where a rechallenge or re-exposure to clozapine have been published after cardiomyopathy.[17 18] In one case, clozapine was rechallenged after

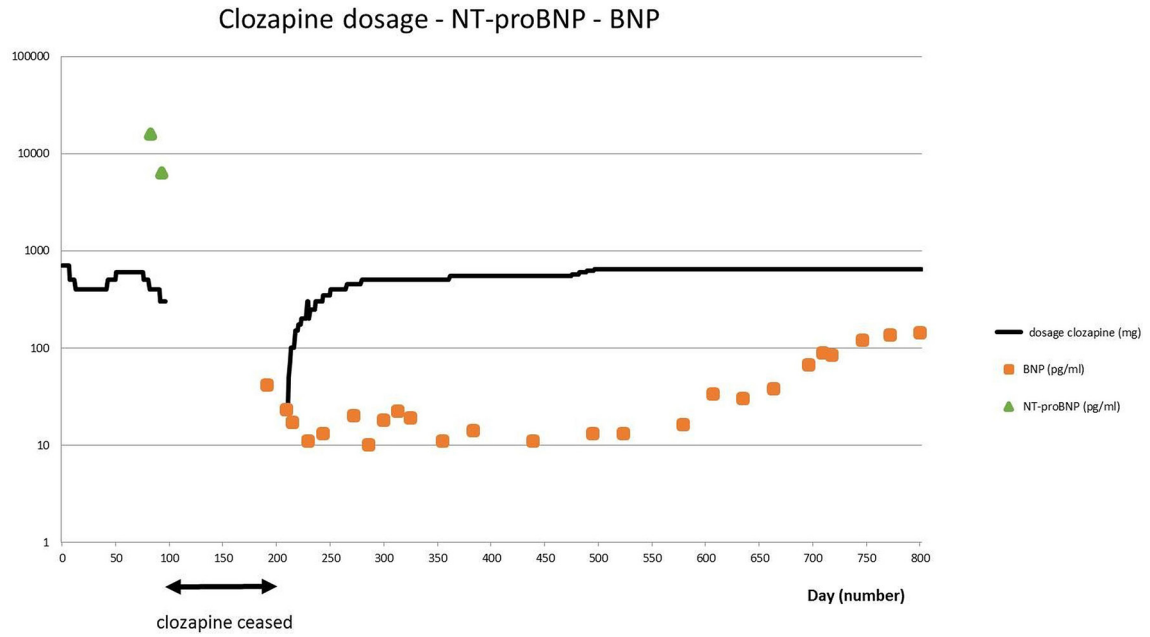

Figure 5 Clozapine dosage, NT-proBNP and BNP.

a cardiomyopathy with an ejection fraction of 35%–40% and a dilated left ventricle. A repeat echocardiogram after 1 month of clozapine was made, and since that time, the left ventricle ejection fraction has been within normal limits. Therefore, the rechallenge was considered to be successful.[18] In the other case, a 31-year-old man developed cardiomyopathy while using clozapine. Physical improvement was seen when clozapine was stopped. Re-administration of clozapine caused a recurrence of dilated cardiomyopathy. In this case, rechallenge of clozapine was unsuccessful.[17] Our case shows that re-exposure after a possibly related dilated cardiomyopathy was successful for at least 2 years. Case reports for patients with multiple risk factors can be helpful for benefit–risk analysis for future patients. Clozapine can be re-initiated after cardiomyopathy with multiple risk factors under strict monitoring of cardiac function.

Learning points

- The cause of a dilated cardiomyopathy can be multifactorial, and for refractory schizophrenic patients, it is a difficult decision whether to continue or discontinue clozapine therapy.
- Case reports regarding re-exposure after possibly related adverse events can be helpful for clinical decision-making and risk–benefit analysis.
- In this case, clozapine was continued during cytostatic treatment of breast cancer.
- Based on shared decision-making, re-exposure of clozapine after successful heart failure treatment was preferred to improve the patients' quality of life and was successful.

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Competing interests None declared.

Patient consent Obtained.

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