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Case Report

Long-Term Clozapine Treatment and Chronic Lymphocytic Leukemia: A Case Report

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ABSTRACT

Background: Clozapine is an a typical antipsychotic drug, without extrapyramidal side effects, showing potential for the treatment of resistant forms of schizophrenia, which affects approximately 30% of patients diagnosed with this disease. The risk of agranulocytosis encountered in patients using clozapine is not the only reason that psychiatrists hesitate. Moreover has been observed a correlation between clozapine use and the development of lymphomas and even acute leukemia in some patients.

We present a 47-years-old patient diagnosed with Treatment-Resistant Schizophrenia (TRS) on clozapine medication for almost eight years, who developed Chronic Lymphocytic Leukemia (CLL). We also performed a literature review using the pubmed database regarding the hematological malignancy induced effects of clozapine in long-term treatment-resistant schizophrenia patients.

In our patient, interruption of clozapine treatment was followed by severe acute psychosis and agitation, but the reuse of clozapine stabilized him. We treated the patient with chemotherapeutic agents without interrupting clozapine, and we did not observe any additional hematological worsening during the treatment.

Conclusion: Clozapine is the drug of choice for patients with TRS. Numerous studies have demonstrated a correlation between clozapine use and the development of hematological malignancies. In such a situation, it is strongly recommended to perform blood tests on TRS patients while receiving therapy, bearing in mind that each of them may be at risk of developing hematological malignancies.

Keywords: Clozapine; Hematological malignancies; Schizophrenia; Treatment-resistant schizophrenia; Chemotherapy

INTRODUCTION

Clozapine, an atypical antipsychotic drug, without extrapyramidal side effects, was discovered in 1956 and launched on the market in the early 1970s, showing potential for the treatment of therapy-resistant forms of schizophrenia (TRS), which affects about 30% of patients with schizophrenia [1]. Although approved by the FDA for the treatment of these severe forms of schizophrenia (persistent moderate to severe delusions or hallucinations despite two or more clinical trials with other antipsychotic drugs, and/or are at high risk for suicide), again this preparation arouses "fear" among psychiatrists in its use due to the hematological side effects it presents [2]. The risk of agranulocytosis (absolute neutrophil count less than 0.5×10^9 cells/L) encountered in patients using this preparation and first described after 1975, is not the only reason that makes psychiatrists hesitate. A correlation has also been observed between its use and the appearance of lymphomas, and in some patients, even acute leukemia [3-5]. We present the case of a patient with TRS on long-term clozapine treatment who was diagnosed with Chronic Lymphoid Leukemia (CLL). We conducted a literature review to better evaluate the findings of clozapine use as a factor inducing hematological malignancies.

CASE PRESENTATION

We report the case of a 47-year-old male patient who had been suffering from schizophrenia since the age of 18 years. The diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) at our Hospital of

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Mental Disorders, UHC "Mother Teresa". The patient had a history of multiple hospitalizations and was on treatment with several antipsychotic regimens until 2014, when he was diagnosed with Treatment-Resistant Schizophrenia (TRS) and was started on clozapine at a daily dosage of 200 mg. Since then, he has been clinically stable with no hospitalization, and his blood counts were in the normal range until May 2017 when he presented with enlarged left unilateral cervical lymph nodes 2.5 cm × 3.0 cm with no splenomegaly. A CT scan with enhanced contrast revealed enlarged cervical lymph nodes only on the left side. The biopsy of the lymph node resulted in the diagnosis of chronic lymphocytic leukemia. He was diagnosed as Stage I, Binet A CLL, and was on "watch and wait" with regular follow-ups. In late December 2021, he stopped taking treatment with clozapine without medical recommendations and two weeks later he was hospitalized in the Hospital of Mental Disorders with severe psychosis, hallucinations, and aggressive comportment.

During hospitalization, he complained of extreme fatigue, weight loss >10% over three months, and drenching night sweats. Physical examination revealed, skin pallor and enlarged bilateral cervical, axillary, and inguinal lymph nodes, and an enlarged spleen. In the complete blood count, he presented HB 10 g/dl, WBC 210,000/mm^3 (lymphocytes 97%), and PLT 155,000/mm3. He presented direct and indirect coombs tests that were slightly positive (+). Bone marrow aspiration resulted with 90% of mature lymphocytes. Flow cytometry from bone marrow aspiration demonstrated monoclonal proliferation of B cell mature lineage presenting 93% of all the cells and showing CD19+(95%), CD 20+(50%), CD5+(50%), CD23+(30%), CD45 +(100%), Lambda+(50%). The patient resulted with beta 2-MG 3.7 mg/L, TP53 negative. Therefore, we decided to start the treatment for CLL. He was on concomitant therapy with clozapine during the six R-CHOP cycles of treatment, and never developed febrile neutropenia. He continued on clozapine 200 mg daily. After treatment, the patient was in complete hematological remission and was mentally stable. The patient is currently undergoing follow-up (Figure 1).

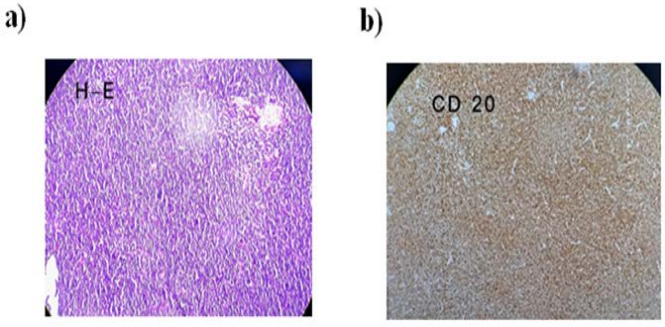

Figure 1: Bone marrow immuno histochemistry showing strong positivity for a) H-E staining and b) CD 20 positive Courtesy of Prof. Laert Berdica.

RESULTS AND DISCUSSION

Schizophrenia is a mental disease that affects approximately 0.5-0.8% of the world's population [6]. When discussing about TRS, we refer to schizophrenia patients who continue to have symptoms and poor outcomes despite the treatment given to them, and it occurs in approximately 30% of patients diagnosed with schizophrenia [7]. It was agreed to consider as TRS all the patients diagnosed with schizophrenia showing inadequate response to two different antipsychotics, each taken with adequate dose and duration for at least 6 weeks [8]. Meltzer in 1992 concluded that 60-70% of cases of TRS responded to clozapine, and a few years later, Wahlbeck (1999), in a systematic review and meta-analysis of 2,530 participants enrolled in 30 clinical trials demonstrated that patients on clozapine had more clinical improvement and fewer relapses compared to the other treatments. Chaos and Lieberman, in another meta-analysis of 12 controlled studies with 1,916 independent patients involved, studying the effectiveness of second generation antipsychotics in TRS patients, in 2001, will demonstrate the superiority of the efficacy and safety of clozapine in comparison with other treatments [9-11].

Despite the efficacy and safety profile of clozapine, hematological abnormalities are frequently encountered during treatment with antipsychotic drugs. It is mostly mild and of no clinical significance, but it is important to mention that in a small group of patients, we can encounter a potentially life-threatening hematological side effect, such as agranulocytosis. Although rare, it is essential to promptly diagnose and manage this disease. Multiple case reports have described patients on clozapine developing hematological neoplasms. There have been several case reports and clinical studies [12-15]. Melzer in 2015, in a letter written to the editor of Australian & New Zealand Journal of Psychiatry, showed that from 221 patients diagnosed with TRS and being treated with clozapine, five developed lymphoma.

Basil and Chretien conducted in 2021 a pharmacovigilance study using VigiBase, the WHO pharmacovigilance database. They concluded that clozapine was significantly associated with malignant lymphoma and leukemia, and the results were 493 malignant lymphoma cases and 275 leukemia cases, diagnosed from 140,226 clozapine associated reports. Patients diagnosed with hematological malignancies were younger in the clozapine-treated group than in the non-clozapine-treated group. In a nationwide case-control study conducted in Finland, Tiihonen J et al. evaluated the risk of hematological malignancies in patients treated with long-term clozapine and demonstrated that the cumulative incidence of hematological malignancies during the mean follow-up of 12.3 years of 13,712 patients treated with clozapine for 102 cases. The number of patients who developed hematologic malignancies was 375, of which 305 were diagnosed with lymphomas 42 with leukemia, 22 with multiple myeloma, and 6 were unspecified. The study revealed a dose response relationship between clozapine and hematological malignancies.

CONCLUSION

We have concluded that clozapine is significantly associated with the risk of developing hematologic malignancies, mostly lymphomas and leukemia's, and its long- term use has a higher effect on mortality due to lymphoma and leukemia. We have to accurately study the risk benefit balance of clozapine, and patients should be assessed carefully using the lowest possible dose of clozapine. All the mental health clinicians should be aware of and be vigilant for any signs or symptoms suggesting hematological malignancies in patients treated with clozapine.

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PATIENT CONSENT

We confirmed that the guidelines on patient consent were met, and informed consent was obtained from the patient reported here. We certify that formal approval for reporting this case was obtained from the patient described here. We are able to verify the validity of the results reported, all data related to the case reported here are preserved in the archives of the inpatient unit of Department of Internal Medicine, Service of Hematology, and from the department of Statistics at UHC "Mother Teresa" Tirana, Albania.

CONFLICT OF INTEREST

The authors declare no competing financial interest.

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