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Case Report

Clozapine related risk of lymphoid malignancies in Treatment-Resistant Schizophrenia – A case report and review of the literature

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Abstract: Clozapine is an atypical 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/Small Cell Lymphoma (CLL/SCL). 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. 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, Chemotherapy, Agranulocytosis

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1 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 affect s about 30% of patients with schizophrenia (de Bartolomeis et al., 2022). 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 (Moore et al., 2007). 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 (de Leon et al., 2022; Chrétien et al., 2021; Tiihonen et al., 2022). We present the case of a patient with TRS who was diagnosed with Chronic Lymphoid Leukemia/Small Cell Lymphoma (CLL/SCL). We conducted a literature review to better evaluate the findings of clozapine use as a factor inducing hematological malignancies.

2 Case report

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 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 x 3,0 cm with no splenomegaly. A CT scan with enhanced contrast revealed enlarged cervical lymph nodes only on the left side. He was diagnosed with Chronic Lymphocytic Leukemia/ Small Cell Lymphoma (SCL/LLC), and was on "watch and wait" with regular follow-up s. 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/mm3 (lymphocytes 97%), and PLT 155,000/mm3. He had direct and indirect Coombs tests that were slightly positive (+). Therefore, we decided to start the treatment for CLL/SCL. He was on concomitant therapy with clozapine during the six

R-CHOP cycles of treatment, and then never developed febrile neutropenia and continued on clozapine 200 mg daily. After treatment, the patient was in complete hematological remission and was mentally stable on clozapine treatment. The patient is currently undergoing follow-up.

3 Review of evidence

Schizophrenia is a mental disease that affects approximately 0.5 -0.8% of the world's population (Saha et al., 2005). 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 (de Bartolomeis et al., 2022). It was agreed to consider as TRS allall the patients diagnosed with schizophrenia showing inadequate response to two different antipsychotics, each taken with adequate dose and duration for at least 6 weeks (Kane et al., 2019). Meltzer in 1992 concluded that 60-70% of cases of TRS responded to clozapine, and a few years later, Wahlbeck et al. (1999), in a systematic review and meta-analysis of 2,530 participants enrolled in 30 clinical trial's demonstrated that patients on clozapine had more clinical improvement and fewer relapses compared to the other treatments. Chakos et al. (2001) in another meta-analysis of 12 controlled studies with 1,916 independent patients involved, studying the effectiveness of second generation antipsychotics in TRS patients, will demonstrate the superiority of the efficacy and safety of clozapine in comparison with other treatments. 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 (Ali et al., 2014; Augustine and Maroules, 2021; Sopko and Caley, 2010) and clinical studies.

Meltzer 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 lymphomas (Meltzer, 2016). Chrètien et al. (2021) conducted 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 et al. (2022) 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.

4 Conclusions

We have concluded that clozapine is significantly associated with the risk of developing hematologic malignancies, mostly lymphomas and leukemias, 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.

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 Haematology, and from the department of Statistics at UHC "Mother Teresa" Tirana, Albania Contributor information.

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Conflict of interests

The authors declare no conflicts of interests.

References

Ali, M. S., Lehmann-Waldau, F., & Taikato, R. M. (2014). Continuation of clozapine in a patient with lymphoma. *The Australian and New Zealand Journal of Psychiatry, 48*(11), 1066-1067. https://doi.org/10.1177/0004867414539399

Augustin, N. B., & Maroules, M. (2021). Hyperleukocytosis during clozapine treatment: A rare presentation of B-cell Acute lymphoblastic leukemia. *Leukemia Research Reports, 15*, 100253. https://doi.org/10.1016/j.lrr.2021.100253

Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., & Sheitman, B. (2001). Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a

review and meta-analysis of randomized trials. *The American Journal of Psychiatry, 158*(4), 518-526. https://doi.org/10.1176/appi.ajp.158.4.518

Chrétien, B., Lelong-Boulouard, V., Chantepie, S., Sassier, M., Bertho, M., Brazo, P., Humbert, X., Alexandre, J., Fedrizzi, S., & Dolladille, C. (2021). Haematologic malignancies associated with clozapine v. all other antipsychotic agents: a pharmacovigilance study in VigiBase®. *Psychological Medicine, 51*(9), 1459-1466. https://doi.org/10.1017/S0033291720000161

de Bartolomeis, A., Barone, A., Vellucci, L., Mazza, B., Austin, M. C., Iasevoli, F., & Ciccarelli, M. (2022). Linking Inflammation, Aberrant Glutamate-Dopamine Interaction, and Post-synaptic Changes: Translational Relevance for Schizophrenia and Antipsychotic Treatment: a Systematic Review. *Molecular Neurobiology, 59*(10), 6460-6501. https://doi.org/10.1007/ s12035-022-02976-3

de Leon, J., De Las Cuevas, C., Sanz, E. J., Ruan, C. J., & Correll, C. U. (2022). Clozapine and the risk of haematological malignancies. The lancet. *Psychiatry, 9*(7), 537-538. https://doi.org/ 10.1016/S2215-0366(22)00154-7

Kane, J. M., Agid, O., Baldwin, M. L., Howes, O., Lindenmayer, J. P., Marder, S., Olfson, M., Potkin, S. G., & Correll, C. U. (2019). Clinical Guidance on the Identification and Management of Treatment-Resistant Schizophrenia. The *Journal of Clinical Psychiatry, 80*(2), 18com12123. https://doi.org/10.4088/JCP.18com12123

Meltzer H. Y. (1992). Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophrenia Bulletin, 18*(3), 515-542. https://doi.org/10.1093/schbul/18.3.515

Meltzer, M. (2016). Lymphoma developing during clozapine therapy. *Australian & New Zealand Journal of Psychiatry*, *50*(5), 498-499. doi: 10.1177/0004867415623860

Moore, T. J., Cohen, M. R., & Furberg, C. D. (2007). Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Archives of Internal Medicine*, *167*(16), 1752-1759. https://doi.org/10.1001/archinte.167.16.1752

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS Medicine, 2*(5), e141. https://doi.org/10.1371/journal.pmed.0020141

Sopko, M. A., & Caley, C. F. (2010). Chronic leukocytosis associated with clozapine treatment. *Clinical Schizophrenia & Related Psychoses, 4*(2), 141-144. https://doi.org/10.3371/ CSRP.4.2.6

Tiihonen, J., Tanskanen, A., Bell, J. S., Dawson, J. L., Kataja, V., & Taipale, H. (2022). Long-term treatment with clozapine and other antipsychotic drugs and the risk of haematological

malignancies in people with schizophrenia: a nationwide case-control and cohort study in Finland. The lancet. *Psychiatry, 9*(5), 353-362. https://doi.org/10.1016/S2215-0366(22)00044-X

Wahlbeck, K., Cheine, M., Essali, A., & Adams, C. (1999). Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *The American Journal of Psychiatry, 156*(7), 990-999. https://doi.org/10.1176/ajp.156.7.990