**SAS Journal of Medicine**
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

**Medicine**

# Polycythemia under Clozapine: A Case Study

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**DOI:** https://doi.org/10.36347/sasjm.2024.v10i09.037 | **Received:** 19.08.2024 | **Accepted:** 25.09.2024 | **Published:** 28.09.2024

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**Abstract** **Case Report**

Clozapine is widely recognized as a last-resort treatment for resistant schizophrenia, due to its efficacy in reducing persistent symptoms and lowering the risk of suicidal behavior. However, its use is limited by severe side effects, including hematological complications such as agranulocytosis. A less documented but significant complication is clozapine-induced polycythemia. This case study explores the development of polycythemia in a patient undergoing clozapine treatment for refractory schizophrenia. Despite the reduction of clozapine doses, polycythemia persisted, necessitating continued treatment due to the lack of alternative therapeutic options. The patient's hematological abnormalities were managed through regular phlebotomies, and close collaboration between psychiatric and hematological services. This case emphasizes the importance of rigorous hematological monitoring in patients on clozapine and calls for further research into its effects on the hematopoietic system, particularly concerning polycythemia. The mechanisms underlying this association are not well understood but may involve immune-mediated responses, bone marrow alterations, and metabolic changes, necessitating multidisciplinary management for optimal patient care.

**Keywords**: Clozapine-induced polycythemia, Refractory schizophrenia, Hematological monitoring, Multidisciplinary management, Alternative therapeutic options.



## INTRODUCTION

Schizophrenia, a severe mental disorder characterized by abnormal interpretations of reality, leads to hallucinations, delusions, and disorganized thinking, significantly impairing daily functioning. These symptoms are often linked to abnormalities in the brain's dopaminergic pathways. Managing schizophrenia requires lifelong treatment, and early intervention can improve long-term outcomes. Among the treatments, clozapine stands out for treatment-resistant cases, reducing persistent symptoms and the risk of suicidal behavior. However, its use is limited by severe side effects, such as agranulocytosis, requiring regular monitoring.

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm that causes an excessive increase in red blood cells in the peripheral blood, a condition known as polycythemia. This disease is primarily due to a JAK2 gene mutation, leading to uncontrolled blood cell proliferation. While PV usually manifests with symptoms like fatigue, headaches, and dizziness, it can also be asymptomatic and incidentally discovered during routine lab tests. A diagnosis of polycythemia is made when no secondary cause is evident [1]. PV management often involves regular phlebotomies to reduce hematocrit levels and, in more severe cases, cytoreductive medications to prevent thromboembolic complications.

While clozapine effectively treats resistant schizophrenia, it can sometimes lead to severe side effects, including secondary polycythemia vera (PV). This form of PV, induced by clozapine, is a rare but well-documented complication in the literature. Clozapine may cause an abnormal increase in red blood cell production, possibly due to its effect on inflammatory cytokine levels and its ability to stimulate erythropoiesis [2]. This excessive proliferation of red blood cells can lead to blood hyperviscosity, increasing the risk of thromboembolic complications.

Recognizing clozapine-induced secondary PV is crucial for the therapeutic management of patients. In such cases, clozapine treatment may need to be re-evaluated, considering alternative therapies or implementing measures to manage polycythemia, such as regular phlebotomies or cautious use of cytoreductive drugs. Close hematological monitoring is essential to

detect early signs of polycythemia and prevent serious complications associated with this condition.

## OBJECTIVES

The objective of this study is to explore, through a clinical case, the potential relationship between clozapine treatment and the onset of polycythemia. Although highly effective for treatment-resistant schizophrenia, clozapine can lead to rare side effects such as polycythemia. This clinical case aims to analyze data to determine if this condition is related to clozapine use while offering recommendations for optimal management of patients on this treatment. This study contributes to a better understanding of the hematological risks associated with clozapine.

## CLINICAL CASE

Our patient, a 41-year-old man, has a complex medical history, including a head injury at age 5 and 19 years of treatment for refractory schizophrenia. Over the years, he was hospitalized numerous times and received various typical and atypical antipsychotic treatments without symptom remission. Due to the inefficacy of these treatments, he was eventually deemed eligible for clozapine treatment, often used as a last resort in resistant schizophrenia cases.

Despite the introduction of clozapine, the patient showed only slight clinical improvement. Various therapeutic combinations were tried simultaneously, eventually achieving a satisfactory result with the clozapine-aripiprazole combination. During routine follow-up, a progressive increase in white blood cells, platelets, and hemoglobin was observed in several blood counts, leading to a consultation with the hematology department. Investigations revealed a diagnosis of polycythemia vera, a myeloproliferative neoplasm requiring monthly phlebotomies to manage the excess red blood cells.

Despite reducing clozapine doses and switching to another atypical antipsychotic, no hematological improvement was observed. However, discontinuing clozapine was not an option due to the severe schizophrenia, which had not responded to any other antipsychotic treatment. Clozapine remained the only treatment capable of partially controlling the psychiatric symptoms, even though it did not lead to complete improvement. Given the severity of the schizophrenia and the risks associated with stopping clozapine, the approach was to continue this treatment while implementing close hematological monitoring. Regular blood counts were initiated to monitor the progression of polycythemia in collaboration with the hematology department. This multidisciplinary approach allowed managing the hematological risks while maintaining the necessary treatment for schizophrenia, illustrating the delicate balance between managing severe side effects and the imperative need to control a resistant psychiatric disorder.

## DISCUSSION

Scientific literature primarily focuses on the link between clozapine and agranulocytosis or neutropenia, potentially fatal complications requiring constant patient monitoring. However, the association of clozapine with other hematological parameters, such as increased leukocytes, granulocytes, hemoglobin, and platelets, is less documented but deserves more attention. In our patient's case, an unusual tendency for elevated blood parameters was observed, suggesting that clozapine might have a direct or indirect effect on the hematopoietic system, leading to abnormalities such as polycythemia vera.

A thorough evaluation of this clinical case allowed us to conclude that it involved two distinct nosological entities: the psychiatric condition under treatment revealing polycythemia vera (PV). Traditionally, PV is considered a diagnosis of exclusion, confirmed only in the absence of reactive conditions that could explain the increase in blood cells. However, this particular case led us to explore the hypothesis of a possible relationship between clozapine treatment and the onset of a reactive condition such as thrombocytosis observed in this patient.

The mechanism by which clozapine could induce blood dyscrasias, such as polycythemia or thrombocytosis, remains largely unknown and is still the subject of ongoing research. It is known that clozapine has been associated with bone marrow suppression and accelerated neutrophil apoptosis, which can have significant repercussions on blood cell production. An interesting hypothesis is that of an immune-mediated response, which could be responsible not only for agranulocytosis, a well-documented complication of clozapine, but also for other hematological abnormalities, such as thrombocytosis or thrombocytopenia. These immune responses could play a key role in the underlying mechanisms of these dyscrasias [3].

Reviewing the few cases reported in the literature shows that clozapine can cause severe hematological effects beyond agranulocytosis. For example, three cases have been described where patients on clozapine developed pancytopenia, a condition in which all blood cell lines are reduced, highlighting the potentially extensive effects of clozapine on bone marrow [4]. Additionally, an article published in the British Medical Journal suggests that clozapine may have a direct effect on bone marrow hematopoietic stem cells, triggering reactions resembling acute myeloid leukemia or a myeloproliferative disorder, which could explain the occurrence of polycythemia vera in our patient [5].

Further exploration of the literature reveals that several studies have also highlighted clozapine's potential impact on iron metabolism and erythropoiesis

regulation. Recent research has suggested that clozapine could alter iron metabolism, leading to an increase in erythropoietin, a hormone that stimulates red blood cell production [6]. This alteration could contribute to polycythemia by increasing red blood cell production independently of traditional PV mechanisms. Additionally, a study showed that some patients on clozapine develop insulin resistance, a factor that could indirectly influence erythropoiesis by promoting an increase in erythropoietin levels [7].

These data suggest that clozapine's effect on polycythemia could be multifactorial, involving immune responses, bone marrow alterations, and systemic metabolic changes. It is thus essential for clinicians to consider these various potential pathways when monitoring patients on clozapine, especially those presenting with hematological abnormalities. This holistic approach could not only improve the management of hematological side effects but also allow a better understanding of the complex mechanisms by which clozapine affects the blood system.

Thus, although clozapine is an essential therapeutic option for patients with resistant schizophrenia, this case highlights the need for rigorous hematological monitoring, not only to detect agranulocytosis but also to identify other potential blood abnormalities. This particular case also raises important questions about the need for further research to better understand clozapine's hematological effects and to determine whether polycythemia vera could, in some cases, be a secondary complication of clozapine treatment.

## CONCLUSION

In conclusion, this case study highlights the complexity of the hematological side effects associated with clozapine treatment, including the rare but significant occurrence of polycythemia vera (PV). While clozapine is indispensable for managing resistant schizophrenia, its impact on the hematopoietic system requires special attention. The underlying mechanisms of this association remain poorly understood, but hypotheses include immune-mediated responses, alterations in iron metabolism, and a direct influence on bone marrow hematopoietic stem cells.

This case emphasizes the importance of rigorous hematological monitoring in patients on clozapine, as well as the need for further research to elucidate the mechanisms involved. A multidisciplinary management approach, involving both psychiatrists and hematologists, is essential to balance the benefits of treatment with the management of potential risks, ensuring optimal patient care.

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