Case Report

Clozapine-induced bicytopenia and possible cytochrome P450 inhibition: a rare case report in a male patient with schizophreniform disorder

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ABSTRACT

Clozapine is a second-generation antipsychotic with proven efficacy in treatment-resistant schizophrenia, but its use is constrained by serious hematologic side effects, notably agranulocytosis. While bicytopenia denotes simultaneous reduction in two blood cell lines which is an uncommon and potentially underrecognized adverse event during clozapine therapy.

We report a case of a 17-year-old male diagnosed with schizophreniform disorder who developed clozapine-induced bicytopenia. After inadequate response to paliperidone 6 mg/day, quetiapine 300mg/day, clozapine was initiated and titrated up to 200 mg/day over 14 days. The patient showed symptomatic clinical improvement; however, two weeks after initiation, he developed fever and laboratory evaluation revealed leukopenia (White blood cell 3500/mm³, Absolute neutrophil count 1435/mm³), while red blood cell count and platelet count remained within normal limits initially. Clozapine was promptly discontinued. Despite partial recovery in WBC and ANC, RBC and Hb levels continued to decline with values reaching 9.9 g/dL and 3.54 million/iL, respectively. Hematologic workup including lactate dehydrogenase (LDH), direct and indirect Coombs tests, and absolute reticulocyte count excluded hemolysis or autoimmune etiology. The patient was subsequently started on roxadustat 70 mg, an erythropoiesis-stimulating agent. Hematologic parameters normalized within four weeks. At the same time patient was suffering from inflammatory skin condition and was being treated with triazole antifungal. In this case, systemic inflammation and a potential drug interaction with itraconazole at a dosage of 65 mg, two tablets daily (total daily dose: 130 mg); may have been contributing factors to clozapine-induced bicytopenia.

This case underscores the importance of extending routine hematologic monitoring in patients receiving clozapine beyond white blood cell (WBC) and absolute neutrophil count (ANC) to include comprehensive blood count parameters, enabling early detection of rare hematologic abnormalities and prevention of serious complications.

Key word: *Clozapine, Bicytopenia, Agranulocytosis, Cytochrome P450 inhibition, Drug-induced bone marrow suppression, Schizophreniform disorder.*

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INTRODUCTION

Clozapine is an atypical antipsychotic recognized for its superior efficacy in the management of treatment-resistant schizophrenia (TRS).[1] It is often considered the gold standard for patients who do not respond adequately to at least two other antipsychotics. Despite its clinical advantages, the use of clozapine is often limited due to its potentially serious adverse effects.

One of the most significant and potentially life-threatening complications of clozapine therapy is

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agranulocytosis, a condition characterized by a severe reduction in neutrophil count. The incidence of agranulocytosis is estimated to be around 0.8-1% in clozapine-treated patients, with the highest risk occurring within the first 18 weeks of treatment. [2] Other hematologic effects include leukopenia, neutropenia, anemia, and in rare cases, pancytopenia.[3]

Pancytopenia refers to a simultaneous reduction in all three major blood cell lines-red blood cells (RBCs), white blood cells (WBCs), and platelets-while bicytopenia denotes a concurrent decrease in any two of these lineages, most commonly RBCs and WBCs.[4] The prevalence of clozapine-induced pancytopenia and bicytopenia is extremely low, with available data limited primarily to isolated case reports rather than large-scale epidemiological studies[4,5].

The exact mechanism of clozapine-induced bone marrow suppression remains unclear. Two major hypotheses have been proposed: clozapine or its reactive nitrenium ion metabolites may exert cytotoxic effects on hematopoietic progenitor cells within the bone marrow which is direct toxicity. Another is immune-mediated response-clozapine may act as a hapten, binding to neutrophils or their precursors and triggering an immune response that leads to targeted destruction.[6] Both mechanisms could result in suppression of granulocyte and erythrocyte lineages.

This case represents a rare instance of clozapine-induced bicytopenia, highlighting the clinical challenges and considerations in managing clozapine-induced hematologic side effects.

CASE REPORT

A 17-year-old male was admitted to the psychiatry ward of a tertiary care hospital with symptoms of self-muttering, suspiciousness, incoherent speech and social withdrawal. During the hospital stay of 3 months, he developed bizarre delusions, including beliefs that his internal organs were being displaced or removed, his stomach was being emptied, and his organs were being sold. Based on clinical evaluation, he was diagnosed with schizophreniform disorder. He scored 114 on Positive and Negative Syndrome Scale (PANSS); (Positive symptoms score 31, Negative symptoms score 34, General psychopathology score 49), which indicates extremely severe illness.

Baseline investigations, including complete blood count (CBC), random bloodglucose, serum creatinine, thyroid profile, and liver function tests, were within normal limits. The patient was started on paliperidone 6 mg/day. As symptoms persisted, quetiapine was introduced and gradually titrated to 300 mg/day. After approximately one month with limited clinical improvement, quetiapine was tapered, and clozapine was initiated. At the same time patient was suffering from a skin condition. Consultation from dermatology was taken, he was diagnosed as suffering from tinea cruris and was being treated with itraconazole, Hydroxyzine hydrochloride, rupatadine, isotretinoin and topical retinoid.

Following baseline blood testing (Day 0), clozapine 12.5 mg/day was started (Day 1), as shown in Figure 1. On Day 7, repeat CBC parameters remained within normal limits. The patient's psychotic symptoms showed symptomatic improvement with gradual dose escalation of clozapine to 200 mg/day over 14 days. Patient developed fever 2 weeks after starting clozapine which subsided after 4 days, although no definitive source of infection or alternative etiology was identified at the time.On Day 14, a repeat CBC revealed a drop in WBC count from 9500 to 3500/mm^3, neutrophil count from 5225 to 1890/ mm^3, and hemoglobin from 13 g/dL to 11.8 g/dL. On the following day, there was a continued drop in neutrophil count to 1435/ mm^3. Due to the significant leukopenia and neutropenia, clozapine was discontinued immediately, he was getting Paliperidone 6 mg/day.

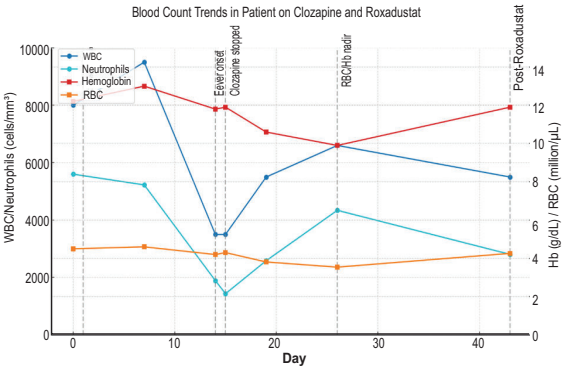

Figure 1. Blood count trends in patient on clozapine and roxadustat

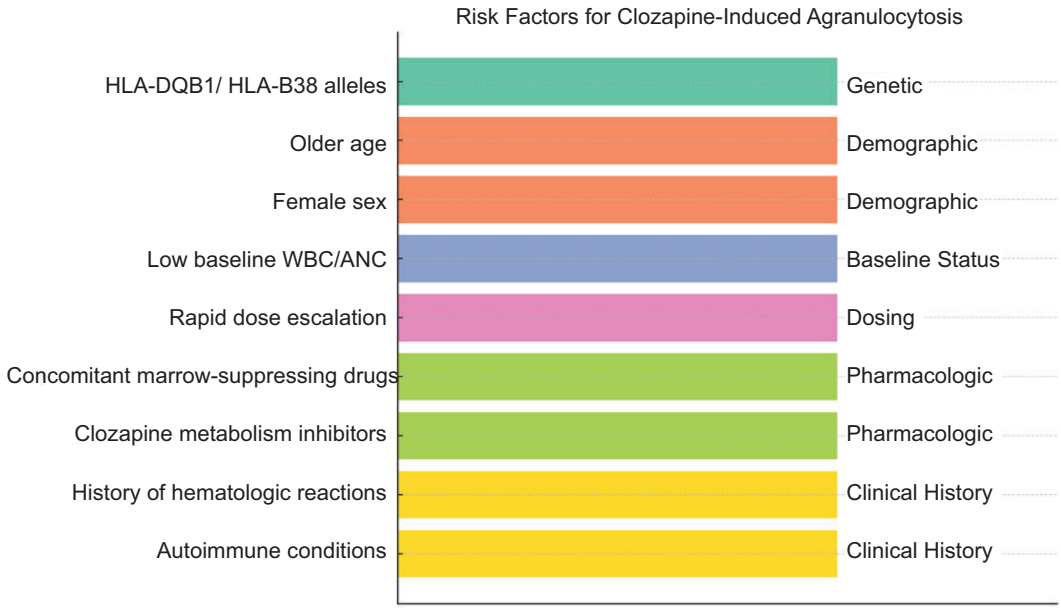

Figure 2. Risk factors for clozapine-induced agranulocytosis

*Horizontal bar chart with categorical color-coding where each bar represented a specific risk factor, and the color indicated its type or category

Following the discontinuation of clozapine, both WBC and neutrophil counts began to rise. However, hemoglobin and RBC count continued to decrease, with values reaching 9.9 g/dL and 3.54 million/iL, respectively. A hematology consultation was sought, and further investigations were conducted to identify other potential causes of anemia.

Comprehensive hematologic evaluation, including lactate dehydrogenase (LDH), direct and indirect Coombs tests, and absolute reticulocyte count, were all within normal limits. Based on the hematologist's recommendation, the patient was started on roxadustat 70 mg, administered on alternate days. After 2weeks of starting roxadustat 70 mg, CBC was repeated which showed Hb% 11.9 g/dL RBC count 4.26 million/ iL along with other parameters within normal limit.

DISCUSSION

Existing literature suggests several risk factors might contribute to clozapine induced bone marrow suppression. Genetic predispositions, particularly certain human leukocyte antigen (HLA) alleles such as HLA-DQB1 and HLA-B38, older age, female sex, low baseline WBC or ANC, rapid dose escalation, systemic inflammation, use of concomitant medications that either suppress bone marrow function or inhibit clozapine metabolism, autoimmune conditions can increase vulnerability to such adverse events (Figure 2).[6] In this case, the presence of an inflammatory skin condition may have been a contributing factor in the development of bicytopenia. Inflammatory states are known to suppress the activity of cytochrome P450 1A2 (CYP1A2), the primary enzyme involved in clozapine metabolism, [7] potentially leading to elevated plasma clozapine concentrations and an increased risk of hematologic toxicity. Additionally, the patient was receiving itraconazole 65 mg/ two tablets daily (total daily dose: 130 mg) a potent inhibitor of cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, CYP1A2, which may have further impaired clozapine clearance. [8] The combined effect of inflammation-induced enzyme suppression and pharmacokinetic interaction with itraconazole likely resulted in increased clozapine exposure, thereby potentiating bone marrow suppression and the observed bicytopenia.

In the present case, the patient developed hematologic abnormalities within 14 days of starting clozapine 200mg/ day, which aligns with the time frame commonly reported in the literature. [7] Although the patient demonstrated

symptomatic improvement in psychosis, he also developed fever while no other clinical signs of infection were noted. In this case, the fever could have several possible causes. Firsly, clozapine can cause fever in the early stages of treatment, often within the first 3 weeks, even without infection. This is thought to be due to an immune-mediated or cytokine-driven response. Secondly, the bone marrow suppression process itself may trigger fever. Another possible explanation caould be the combination of clozapine and itraconazole may have raised clozapine blood levels, increasing the likelihood of systemic side effects, including fever. Laboratory investigations subsequently revealed bicytopenia, specifically leukopenia and anemia, with a preserved platelet count. The early detection of bicytopenia led to the immediate discontinuation of clozapine, in line with established protocols which mandate cessation of the drug if WBC falls below 3000/mm³ or ANC drops below 1500/mm³. [7,9]

Following the withdrawal of clozapine, hematologic recovery occurred in a stepwise fashion. WBC and ANC levels began to normalize within one week, while hemoglobin and RBC counts improved over four weeks. This pattern of recovery is consistent with previous case reports and literature that suggest most cases of clozapine-induced blood dyscrasias resolve within four weeks of drug cessation.[10]

In this case, the absence of hemolysis markers (normal LDH and negative Coombs test), along with a normal reticulocyte count, supported a diagnosis of reduced erythropoiesis rather than increased destruction of red blood cells.[11] The patient was managed with the initiation of roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor, which promotes erythropoiesis.[12] While previous reports indicate that hemoglobin levels typically recover gradually following the discontinuation of clozapine, [4] in our patient, normalization of hemoglobin required adjunctive treatment with roxadustat.

According to the available literature, this appears to be the first documented case of clozapine induced bicytopenia in Bangladesh. This case illustrates the significance of routine haematological monitoring in all patients using clozapine. While current guidelines only focus on WBC and ANC, this case implies that in some individuals, comprehensive monitoring including haemoglobin, RBCs, and platelets may be required to detect rare but dangerous complications such as bicytopenia or pancytopenia. Early detection and management of haematologic toxicity are crucial for avoiding unfavorable outcomes while balancing the therapeutic benefits of clozapine in schizophrenia.

Conclusion

The patient developed bicytopenia within two weeks of clozapine initiation, which resolved following drug discontinuation and initiation of roxadustat. Systemic inflammation and drug interactions were identified as possible contributing factors. This case highlights the importance of early and comprehensive hematologic monitoring during clozapine therapy.

Authors' contribution: SA contributed to conception, design, manuscript Supervision and final approval, LM contributed to literature search and manuscript writing, SS was responsible for patient enrollment, management and follow up, data acquisition.

Consent: Informed consent taken.

Conflicts of interest: Nothing to declare.

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