CASE REPORT

Clozapine and Polycythemia Rubra Vera: A Rare Side Effect or a Separate Medical Condition? – A Case Report

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Abstract
This article highlights the case of a 44-year old Malay man who is diagnosed as having treatment resistant schizophrenia on Clozapine, which then developed Polycythemia Rubra Vera (PRV). It is known that a major side effect for Clozapine is of agranulocytosis, that is a potentially fatal side effect. However, there have been reported disturbances of other hematological parameters, which result in other abnormalities including leucopenia, leucocytosis, thrombocytopenia, thrombocytosis and eosinophilia. Could this case be a pure medical condition of PRV or is there a relation to the effects of Clozapine? In this paper, the aim is to report a case of blood dyscrasia in a 44-year old male who developed Polycythemia Rubra Vera a year after he was observed to have abnormal full blood count results.

Keywords: Clozapine, Polycythemia Rubra Vera, Blood Dyscrasia

Introduction
Clozapine is a second-generation atypical antipsychotic that has been considered a gold standard for schizophrenic patients who have been diagnosed as treatment-resistant to two or more standard antipsychotics. The U.S. Food and Drug Administration (FDA) have approved Clozapine for the treatment of schizophrenia, recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder [1]. Although it has a good response to treating treatment resistant cases of schizophrenia and that it has relatively fewer extrapyramidal side effects compared to the other antipsychotics, the hematological side effects are one of concern when it happens.

Agranulocytosis and Neutropenia are the most serious side effect that causes great concern for psychiatrist and physicians who encounter it. It is established from the premarketing experience and the data obtained from abroad, that the known intrinsic rate of agranulocytosis was estimated to occur between 1 – 2 %, while post-marketing data suggest an incidence of 0.38% [2]. The risk of death nowadays from agranulocytosis is estimated at 1:10000 [3]. Neutropenia risk with Clozapine is found to be approximately 3% with cumulative incidence reports of between the range of 0.9% and 19.8% (8-year cumulative incidence) [4,5]. However, there have not been many reports that mention about other changes in the hematologic parameters. The hematologic changes that have been
described with clozapine also include leukocytosis (0.6%), eosinophilia (1%), and thrombocytopenia/thrombocytosis [6-8].

It is not known if a clear association can be related to polycythemia in the use of clozapine. A case report has seen a similar presentation of clozapine triggering a somatic disease of polycythemia vera [9]. This article aims to report a possible association and trigger between Clozapine and Polycythemia Rubra Vera, in the context of blood dyscrasia.

Case Summary

This case is a 44-year old male who has been diagnosed with Schizophrenia since 1987 when he was 15-years old. He presented in the first instance with being easily irritable with suspiciousness towards others. He also complained of being easily frightened for no apparent reason. There was a deterioration in school performance and with a difficulty in concentration and memory. He had a history of numerous hospitalizations since then and was tried on multiple typical and atypical antipsychotics with no remission in symptoms. In 1997, he had also undergone a course of Electroconvulsive Therapy (ECT). In 2001, he was deemed to fulfill the criteria of treatment-resistant schizophrenia and was commenced on Clozapine. At that point of time, his total white cell count was measured at 13.05 x 10^9/L. He was maintaining well on a dose of 350mg/day Clozapine since 2001. Throughout the course of clozapine, his Total White Cell, Neutrophil, Granulocyte, Lymphocyte, Hemoglobin and Platelet count are shown as in the Figures 1 - 6 below (with average and a 2-period moving average).

![Figure 1. Total White Cell count trend from 2001 to 2016 with a 2-period moving average](image-url)
Figure 2. Neutrophil Count trend from 2002 - 2016 with a 2-period moving average

<table>
<thead>
<tr>
<th>Year</th>
<th>Neutrophil Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>76.00</td>
</tr>
<tr>
<td>2004</td>
<td>63.00</td>
</tr>
<tr>
<td>2013</td>
<td>82.00</td>
</tr>
<tr>
<td>2015</td>
<td>87.93</td>
</tr>
<tr>
<td>2016</td>
<td>84.60</td>
</tr>
</tbody>
</table>

Figure 3. Lymphocyte Count trend from 2002 - 2016 with a 2-period moving average

<table>
<thead>
<tr>
<th>Year</th>
<th>Lymphocyte Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>31.00</td>
</tr>
<tr>
<td>2004</td>
<td>27.55</td>
</tr>
<tr>
<td>2013</td>
<td>22.00</td>
</tr>
<tr>
<td>2016</td>
<td>24.10</td>
</tr>
</tbody>
</table>
Figure 4. Granulocyte Count trend from 2003 - 2015 with a 2-period moving average

Figure 5. Hemoglobin Count trend from 2002 - 2016 with a 2-period moving average
During a routine follow-up in September 2014, an increasing trend in his total white cell, platelet and hemoglobin count was noticed. He was referred for further investigation with the hematology department and was diagnosed with JAK2 polycythemia rubra vera in June 2015 and on monthly venesection. His dosage of clozapine 350mg/day was continued. In October 2015, he was admitted to the hospital after presenting with left sided body weakness and a loss of power in both the left upper and lower limbs (0/5). Computer tomography imaging of the brain showed Right Middle Cerebral Artery (MCA) and Anterior Cerebral Artery (ACA) infarct. His clozapine was subsequently stopped and was started on tablet olanzapine 15mg on noce. Currently, he is bed bound and requires total dependence for his Activities of Daily Living (ADL), with poor rehabilitation potential and poor cognition.

Since clozapine was stopped, there has been improvement in his blood counts. Consultations and medical examinations found no plausible explanation for the blood dyscrasia and myeloproliferative disorder, so it is assumed that it could have been linked to Clozapine, which has caused a somatic mutation. An informed consent was obtained from the patient’s legal guardian prior to reporting this case.

**Discussion**

The mechanism of Clozapine induced blood dyscrasia is relatively unknown. Clozapine has been linked with a suppression of bone marrow and an acceleration of apoptosis of neutrophils [10]. Apart from that, there is also a suggestion of immune mediated response, which causes thrombocytosis or thrombocytopenia and may provide evidence towards the mechanism of agranulocytosis [11].

Most journal articles mention about the link between Clozapine and agranulocytosis/neutropenia. However, it is difficult to rule out the possible association
of Clozapine and its effect on other hematologic parameters such as leukocytes, granulocytes, hemoglobin and platelets. In the figures above, which show the mean levels of each parameter from year-to-year, a significant increase in parameters (TWC, Neutrophil, Granulocyte, Hemoglobin and Platelet) can be seen starting around the year 2011 (Figure 1,2,4,5,6). The only exception is lymphocyte, which shows a decrease in mean levels (Figure 3).

The uncanny trend and elevation of the blood parameters suggests that there are effects of Clozapine on the hematopoietic system, which could lead to the derangements as seen in this patient.

A study reported a case of a 41-year old female who also developed Polycythemia Rubra Vera while on Clozapine. In that case report, they found progressive elevation of blood cells, mainly of the red blood cells line and concluded that there are two different nosologic entities, treatment of the psychiatric condition revealing polycythemia rubra vera [9].

In another case that was reported, a middle-aged male with ICD schizophrenia who failed to respond to neuroleptic medication (haloperidol 25mg/day, chlorpromazine 500mg/day), or olanzapine at 20mg/day for six weeks was started on Clozapine. He complained of nausea fifteen days after commencing clozapine and his platelet count was 454 x 10⁹/L, the erythrocyte sedimentation rate (ESR) 70mm/h and the C-reactive protein was 103. Eight days later, his platelet count has risen to 774 x 10⁹/L. He was apyrexial [8].

An article which was published by the British Medical Journal (BMJ) mentions that a trigger reaction which resembles acute myeloid leukemia or myeloproliferative disorder can be seen due to the direct action on the hematopoietic stem cells of the bone marrow by Clozapine [11].

Conclusion

Frequent and active monitoring remains the mainstay of patients who are treated with clozapine, as the effects on hematological parameters can be various. The possibility of clozapine triggering a somatic mutation reaction causing polycythemia vera could not be ruled out. In this paper, a patient who developed blood dyscrasia during clozapine treatment has been reported and clinicians should exercise caution for the possible occurrence of this risk. It is therefore recommended that there should be active monitoring for patients who are on clozapine according to the Clozapine REMS guidelines [12]. Apart from that, close observation must be done to detect any derangement in the patient’s full blood count which would require a reduction of dose or the withdrawal of clozapine. In the event that there are any unexplained persisting abnormalities in the patient’s blood count, a prompt referral to a hematology specialist should be done to minimize the dangers associated with clozapine.

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Conflict of Interest

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References


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