Case Report
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# Late Onset Agranulocytosis with Clozapine Associated with HLA DR4 Responding to Treatment with Granulocyte Colony-stimulating Factor: A Case Report and Review of Literature

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Agranulocytosis as a side effect of clozapine has been reported to be associated with initial phases of treatment, i.e., first six months. Agranulocytosis with clozapine during the initial phases of treatment has been linked to genetic vulnerability in the form of variations in the human leukocyte-antigen haplotypes. However, there is limited literature on late onset agranulocytosis with clozapine and this has very rarely been linked to human leukocyte-antigen haplotypes vulnerability. In this report we review the existing data on late onset agranulocytosis with clozapine and describe the case of a young man, who developed agranulocytosis with clozapine after 35 months of treatment and was found to have genetic vulnerability in form of being positive for HLA DR4. This case highlights underlying autoimmune immune mechanism in clozapine-induced agranulocytosis and the need for frequent blood count monitoring on clozapine even after the initial 6 months of starting treatment especially in patients with genetic vulnerability to develop this condition.

KEY WORDS: Clozapine; Agranulocytosis; Neutropenia.

## INTRODUCTION

Since the beginning of its use, the heamatological side effects of clozapine in the form of agranulocytosis and neutropenia have been an important issue with the patients and clinicians.[1,2] Available data suggests that overall the incidence rate of agranulocytosis is 0.38% among patients receiving clozapine.[1] Most of the evidence suggests that whenever neutropenia occurs with clozapine, it usually occurs during the early phase of treatment, i.e., highest in first 6 weeks to 18 months after the onset of treatment.[1,3] Due to this, more intense monitoring is suggested during the initial phase of the treatment, i.e., first 18 weeks.[3] However, there are few reports of late onset neutropenia with clozapine after as long as 19 years of use of clozapine.[4-17] Studies have attempted to find out the factors associated with clozapine induced neutropenia. Among the various factors reported to be associated with clozapine induced neutropenia, there is some data to suggest that genetic vulnerability in the form of variations in the human leukocyte-antigen haplotypes predisposes a person to develop neutropenia.[18]

In this report, we present a case of late onset neutropenia with clozapine who on investigation was found positive for human leukocyte antigen (HLA) DR4.

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## CASE

A male patient, University Graduate, smoker, suffering from treatment resistant schizophrenia was started on clozapine at the age of 32 years. Initially he tolerated the dose of clozapine well and showed partial response to clozapine 450 mg/day. Later in view of partial response, trifluoperazine was added and he was stabilized on clozapine 450 mg/day and trifluoperazine 20 mg/day after 9 months of initiation of clozapine. Regular weekly hematological monitoring was done during initial 5 months, followed by monitoring at monthly intervals. He maintained well with this combination for next 26 months. However after this on one occasion he all of a sudden developed high grade fever, which was not associated with any specific systemic signs and symptoms. A haemogram was ordered and it revealed a total leucocyte count of 1,100/mm$^3$

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with neutrophils count of zero. The differential count showed 98% lymphocytes, 1% monocytes and 1% eosinophils, along with hemoglobin level of 13.5 g/dL and platelet count of 1.5 /μl. There was no history of administration of any antibiotics, chemotherapeutic agent, radiotherapy, anti-epileptic medications.

He was immediately hospitalized, all psychotropics were stopped. Physical examination revealed a small ulcer on the prepuce and a tender swelling in his right axilla. He was investigated for possible causes of leucopenia and neutropenia in the form of heamatological malignancies, systemic lupus erythematous, Crohn's disease, rheumatoid arthritis, infections (bacterial, tubercular and viral in the form of human immunodeficiency virus, Epstein-Barr virus (EBV), cytomegalus virus, hepatitis). Investigations in form of serum electrolytes, renal function test, liver function tests, chest X-ray, urine examination (routine and culture sensitivity), blood culture for bacteria and fungus, electrocardiogram and echocardiography did not reveal any abnormality. Serum calcium was 8.24 mg/dl, hepatitis B antigen and hepatitis C antibody were negative. EBV immunoglobulin M antibody (IgM Ab), Widal test, dengue serology (IgM Ab), smear for malaria parasite and ultrasound abdomen did not reveal any abnormality. Venereal Disease Research Laboratory test was found to be negative. The fine needle aspiration cytology of the mass in the axilla was positive for *Proteus mirabilis* which was sensitive to piperacillin and tazobactum. Fever improved after antibiotic treatment was started.

In view of no other detectable cause, the leucopenia and neutropenia were attributed clozapine and the infection was considered to be secondary to the neutropenia. He was further investigated and was found positive for HLA DR4 (DRB1*04) and HLA DQB1*02:01, 1*02:02, 1*03:02. He was managed with granulocyte colony-stimulating factor (G-CSF) at the dose of 5 μg/kg/day for 7 days, along with broad-spectrum antibiotics. Over the period of one week his leucocyte and neutrophil count normalized. In view of the genetic vulnerability clozapine re-challenge was not done and he was managed with a combination of antipsychotics (trifluoperazine and olanzapine) over next one year, with which he showed partial response in terms of improvement in psychotic symptoms.

## DISCUSSION

We searched the PubMed search engine and available data suggests that there is limited literature in the form of case reports of late onset neutropenia and late onset agranulocytosis associated with clozapine,[4-17] with one of the reports showing the association after 19 years of use of clozapine.[5] In a review of literature, authors reported 16 case reports available prior to 2012.[4,8-11,13,16,19-25] The authors themselves reported the 17th case. In our literature search of PubMed, we came across 3 more cases.[10,17,26] The data of all the cases is presented in Table 1. In majority of the case reports, patients were receiving concomitant medications along with clozapine, with valproate (5 cases), risperidone (7 cases) and haloperidol (3 cases) being the commonly used concomitant medications.[4,6,10,13,15-17] In other cases concomitant medication use involved use of antidepressants, anti-tubercular drugs, etc.[7,8,12,15] In 6 cases, late onset agranulocytosis/neutropenia was seen with clozapine monotherapy. In most of these cases, the patients were not rechallenged with clozapine.[4,5,7,9,15,17] Our case developed agranulocytosis while on clozapine for 35 months. In terms of concomitant medication our patient was receiving trifluoperazine, for about 1.5 years prior to development of agranulocytosis. Accordingly it can be concluded that trifluoperazine would not have contributed to agranulocytosis. Our case adds to the limited literature of late onset agranulocytosis/neutropenia and suggests that regular haematological monitoring should be done in patients receiving clozapine. In our case neutropenia improved rapidly over the period of 1 week. The rapid resolution of neutropenia after stoppage of clozapine possibly suggests that the neutropenia was due immune mediated destruction of neutrophils, which resolved with stoppage of offending agent. The Naranjo probability score for our case was 7, indicative of probable association.[27]

Over the years few researchers have attempted to find the risk factors associated with development of clozapine-induced agranulocytosis. The factors identified to have some association with clozapine-induced agranulocytosis include HLA class III genes for tumor necrosis factor (TNF) and heat shock proteins (HSP), increased expression of proapoptotic genes bax $\alpha$, p53, and bik and presence of certain HLA phenotypes. With regard to the HLA class III genes for TNF and HSP it is proposed that the formation of oxidized clozapine intermediates may decrease the survival of granulocytes in individuals who carry clozapine-induced agranulocytosis susceptibility-associated HSP or TNF variants.[28] Increased expression of proapoptotic genes bax $\alpha$, p53, and bik has been linked to oxidative mitochondrial stress in neutrophils of clozapine-treated patients and suggest that free radicals and oxidative stress possibly up-regulate proapoptotic genes and contribute to the induction of apoptosis and clozapine-in-

**Table 1.** Published case reports on late onset neutropenia/agranulocytosis with clozapine

| Author | Age (yr)/ sex | Diagnosis | Dose of clozapine (mg/d) | Type of heamatological abnormality | Duration of clozapine use prior to neutropenia/ agranulocytosis | Concomitant medications | Concomitant physical illness and clozapine associated complications | Remarks | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Voulgari *et al.*[26] | 33/F | Schizoaffective disorder | 400 | TLC: 100<br>ANC: zero | 24 months | Levothyroxine 125 $\mu$g/d | *Streptococcus pneumonia*<br>Venous thromboembolism<br>Allergic vasculitis | G-CSF given | Rechallenge done<br>No complication |
| Velayudhan and Kakkan[17] | 44/F | Paranoid schizophrenia | 150 | TLC: 6,700→700<br>ANC: 4,690→< 100<br>Over 7 days | 60 months | Risperidone 6 mg/d<br>Trihexyphenidyl 4 mg/d | Fever, rigor, swelling of right hand, sore throat, deep vein thrombosis right upper limb | Continued on risperidone 8 mg/d<br>Chlorpromazine 150 mg/d<br>Trihexyphenidyl 2 mg/d<br>Partial remission | Partial remission<br>No rechallenge |
| Cohen and Monden[5] | 42/M | Paranoid schizophrenia<br>Opium abuse | 250 | Two months<br>TLC: 2,500→1,900<br>ANC: 1,000→600 | 228 months | ±Lorazepam 2.5 mg/d | Fever, laryngitis | Aripiprazole 45 mg/d<br>Lorazepam 5 mg/d<br>Full remission | Cell count recovery in one week<br>No rechallenge |
| Raveendranathan *et al.*[10] | 31/F | Paranoid schizophrenia | 325 | TLC: 2,820→2,200<br>ANC: 1,111→198<br>Over two weeks | 24 months (of rechallenge with 325 mg dose) | Risperidone 6 mg/d | Nil | History of neutropenia in past within 3 wks of clozapine dose 325 mg/d<br>TLC: 10,100→6,500<br>ANC (details NA): rechallenge→2nd time agranulocytosis→risperidone 8 mg/d, HPL 30 mg/d, lithium 900 mg/d | Rechallenge (after neutropenia)<br>Treated with G-CSF (in 2nd episode), count normalised in 2 wks |
| Raja *et al.*[9] | 65/M | Schizoaffective disorder | 450 | Over 7 months, progreesive neutropenia | 120 months | Metformin 500 mg/d | Nil | Risperidone 6 mg/d →olanzapine 10 mg/d+ quetiapine 150 mg/d | Cell count recovery in next week<br>No rechallenge |
| Tourian and Margolese[16] | 41/F | Paranoid schizophrenia<br>Tobacco dependence | 100 | Three months (corresponding to increase in lamotrigine dose) | 84 months | Risperidone 1 mg/d<br>Lamotrigine 100 mg/d | Treated with stoppage of clozapine, lamotrigine; G-CSF + | Agranulocytosis associated with increase in lamotrigine dose | Rechallenge done<br>No agranulocytosis |
| McKnight *et al.*[35] | 33/F | Schizoaffective disorder | 96 | 300 | Details NA | Sodium valproate 1,500 mg/d<br>Quetiapine 4,000 mg/d | Nil | HLA – DQB1 testing done | Rechallenge<br>Done<br>No complication after rechallenge |
| Panesar *et al.*[8] | 37/M | Schizoaffective disorder | 108 | Detail NA | TLC: 2,700<br>ANC: 500 | Anti-tuberular medication | Nil | While on anti-tubercular drugs (duration detail NA) | Clozapine rechallenge 500 mg/d<br>No complication after rechallenge |

**Table 1.** Continued

| Author | Age (yr)/sex | Diagnosis | Dose of clozapine (mg/d) | Type of heamatological abnormality | Duration of clozapine use prior to neutropenia/ agranulocytosis | Concomitant medications | Concomitant physical illness and clozapine associated complications | Remarks | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Ghaznavi *et al.*[6] | 55/M | Paranoid schizophrenia | 168 | 750 | ANC: 2,556→1,620, over one month | Valproic acid 1,500<br>Donepezil (dose NA) | Nil | Within one month of starting donepezil | Rechallenge in one week→clozapine increased 500 mg/d in 20 days; donepezil stopped, ANC 2,762→850 in 20 days, risperidone 6 mg/d |
| Manfredi and Sabbatani[7] | 36/M | Severe depressive disorders<br>Personality disturbances<br>Suicidal behaviour | NA | 16 weeks<br>Severe leukopenia sudden onset (TLC: 1,050<br>ANC: 36 cells/ $\mu$L) | 96 HPL | Lithium carbonate 600 mg/d<br>Citalopram 40 mg/d<br>Clomipramine 75 mg/d<br>Lorazepam 2.5 mg/d | Fever (pyrexia of unknown origin) | G-CSF | No rechallenge |
| Small *et al.*[13] | 45/F | Schizophrenia<br>Mild mental retardation<br>Tobacco dependence | 72 | 500 | Sudden, 4,000→1,800, ANC: 2,000→198 | Olanzapine 10 mg/d<br>HPL 150 mg/3 wk<br>Benzopril hydrochloride 20 mg/d | Nil | Clozapine rechallenge 800 mg/d, slow titration over 5 months<br>Lithium added later→increase in TLC, ANC | No complication after rechallenge |
| Thompson *et al.*[15] | 34/M | Paranoid schizophrenia | 36 | 250 | ANC: 1,500/ $\mu$L<br>TLC: 5,840/ $\mu$L | Sod valproate 1,000 mg/d<br>Sertraline 50 mg/d | Nil | While on valproate, SSRI | No rechallenge |
| Bhanji *et al.*[4] | 48/M | Undiff. schizophrenia | 550 | Fall in TLC (7,600→2,900)<br>Drop in neutrophil count (3,000 →1,000) | 17 months (abrupt drop) | Risperidone 5 mg/d<br>Olanzapine 15 mg/d<br>Valproate 750 mg/d<br>Quetiapine 50 mg/d | Nil | Quetiapine associated with idiosyncratic leukopenic reactions - additive toxicity | Clozapine stopped→recovery in 8 days<br>No rechallenge |
| Silvestrini *et al.*[12] | 29/F | Undiff. schizophrenia | 300 | TLC: 2,600<br>ANC: 1,340/mm$^3$ | 60 months | Clomipramine 75 mg/d | Insomnia, shivering, hot flushes, sense of tremor, symptoms of common cold, dry mouth | Thioridazine 350 mg/d olanzapine 20 mg/d, valproate 1,500<br>→ more 2 months<br>Clozapine rechallenge | Cell count-recovery in 2 days<br>Clozapine 500 mg/d<br>Clomipramine 150 mg/d |

M, male; F, female; TLC, total leucocyte count; Nil, no comorbid physical illness; ANC, absolute neutrophil count; G-CSF, granulocyte colony stimulating factor; SSRI, selective serotonin reuptake inhibitors; HLA, human leukocyte antigen; NA, not available; Undiff., undifferentiated; HPL, haloperidol.

duced agranulocytosis.[29] There is lack of consensus for type of HLA phenotype associated with clozapine-induced agranulocytosis. Lieberman *et al.*[30] reported that Ashkenazi Jews exhibiting the phenotype HLA B38, DR4, DQW3 are at an increased risk of agranulocytosis, as are non-Jewish individuals with HLA phenotype B7, DR2, DQ2. They also suggested that specific gene products encoded in the major histocompatibility complex may be involved in mediating drug toxicity. Yunis *et al*.,[31] in an extension of the findings of Lieberman *et al*.,[30] observed that in Ashkenazi patients the susceptibility class II haplotype is DRB1*0402, DQB1*0302, and in non-Jewish patients, DRB1*02, DQB1*0502 and DQA1*0102 were associated with vulnerability to develop clozapine-induced agranulocytosis. However, in another study involving 103 patients with a history of clozapine induced agranulocytosis no significant association was noted between HLA-A, -B, -C, -DR, -DQ, number of neutrophil-specific alloantigens and susceptibility to clozapine-induced agranulocytosis.[32] However, these results were later questioned when emphasis was placed on statistical methodology used for statistical analysis of simultaneous occurrence of multiple HLAs, in an attempt to predict vulnerability to clozapine-induced agranulocytosis.[33] Another study on Israeli Jewish patients showed that HLA B38 conferred susceptibility for clozapine-induced agranulocytosis.[33] Further on combining the data of Lieberman *et al*.[30] and Yunis *et al*.[31], the authors proposed that the gene susceptible for clozapine induced agranulocytosis was located in the HLA-B locus rather than in the DR/DQ region.[34] Recent report has associated increased risk of developing clozapine-induced agranulocytosis in patients with DQB1 genotype.[35] Our case was found positive for HLA DR4 (DRB1*04) and HLA DQB1*02:01, 1*02:02, 1*03:02, suggesting that late onset neurotropenia also may be related to HLA gene susceptibility. In a recent largest study which included, 163 cases authors found association between clozapine induced agranulocytosis and HLA-DQB1 and HLA-B especially two amino acids sequences, i.e., *HLA-DQB1* 126Q and *HLA-B* 158T. However, the authors concluded that they could not distinguish as to whether these amino acids had causal role or just conferred risk.[36]

Besides the genetic vulnerability other factors which have been considered as risk factors for bone marrow suppression with clozapine include increased age (i.e., more than 40 years), female gender, African race, and concomitant medications,[3,37,38] eosinophilia antedating the onset of neutropenia.[39]

The hematopoietic growth factors, G-CSF and granulocyte macrophage colony stimulating factor increase the proliferation and differentiation of myeloid precursor cells. The recombinant human granulocyte growth factor G-CSF (filgrastim) is approved for the correction of severe clozapine-related neutropenia.[40-42] In our patient, immediate discontinuation of clozapine upon diagnosis, prompt initiation of antibiotic therapy, and G-CSF titration managed the early increase in the neutrophil count and the improvement of the patient's clinical presentation.

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