INTRODUCTION
Clozapine is a known risk factor for hematological side effects, such as agranulocytosis and neutropenia; however, blood dyscrasias such as leukocytosis are observed occasionally, which necessitate white blood cell (WBC) monitoring. The incidences of clozapine-induced hematological adverse effect in clinical trials are neutropenia 3%, agranulocytosis 1%, eosinophilia 1%, and leukocytosis are <1%.[1]

Leukocytosis defined as a WBC count >11,000 cells/mm³. It has been associated with clozapine treatment, received less attention in literature. The clinical decision to continue or stop clozapine when leukocytosis develops could be a challenging task. Leukocytosis can occur as a result of physical and emotional stress, such as overexertion, seizure, anxiety, anesthesia, epinephrine administration,[3,4] and infections. Other causes of leukocytosis that may be persistent include medications, splenectomy, hemolytic anemia, and malignancy. Medications that have been reported to cause leukocytosis include corticosteroids, lithium and beta agonist.[5] High smoking rates are also associated with increase total and differential WBC count.[6]

Clinical manifestations of drug-induced leukocytosis include fever, malaise, and easy fatigue, but long-term side effects are unclear. As such, there are no guidelines to advise clinicians, if or when clozapine should be discontinued, if leukocytosis appears.[1] There are no controlled data available to suggest antipsychotics treatment options if clozapine is discontinued because of associated hematological side effects.

CASE REPORT
A 65-year-old, well body built male belonging to low socioeconomic status, has been in psychiatric hospital, Taif in chronic rehabilitation ward since last 14 years. He was diagnosed with schizophrenia 35 years back. Despite being treated with multiple
antipsychotics, he never achieved full remission, so we diagnose him as a treatment-resistant schizophrenia, and accordingly started treatment with clozapine. There is history of smoking since long and subsequently patient developed chronic obstructive pulmonary disease.

Clozapine was started 25 mg once daily, at that time his WBC count was 4490 mm$^3$ and absolute neutrophil count (ANC) 3000 mm$^3$. The clozapine dose was titrated according to the guidelines. At a dose of 100 mg daily of clozapine, WBC count increased to 7500 mm$^3$ and ANC 5000 mm$^3$. Moreover, it was observed that patient’s WBC count was increased in parallel with increase of the clozapine dose. On the 10th week, clozapine dose was increased to 300 mg/day which showed significant rise in WBC count 19,000 mm$^3$ and neutrophil count 15,400 mm$^3$; however, complete blood count remains normal during treatment. Figure 1 depicts the total leukocyte counts findings and corresponding clozapine dose along with the number of days of clozapine use.

On physical examinations, vitals including temperature were within normal limit. The patient did not have any physical complaints or sign of infections but reported easy fatigability. The workup for infection, including chest X-ray, urine analysis, blood culture, stool analysis, hepatitis marker, and HIV testing were negative; other biochemical laboratory tests were normal. Two-dimensional echo was done to rule out myocarditis. Our medical specialist found no evidence of systemic illness and recommends hematological consultation.

It was decided to taper and discontinue clozapine despite improvement of psychotic symptom because repeated consultation and medical examinations found no evidence for the leukocytosis. He was put on amisulpride 200 mg twice a day, after a week that improved his WBC count and ANC decreased and remains in the normal range. The patient was assessed on Naranjo scale, and the score was 6.

**DISCUSSION**

The mechanism of development of leukocytosis due to clozapine remains unknown.[7] One possibility is that clozapine may stimulate the release of certain cytokines including tumor necrosis factor, interleukin (IL)-2, IL-6, and granulocyte colony-stimulating factor.[8] Other possible risk factor may be smoking, being male in this case.

We reviewed the existing literature and many case reports on leukocytosis associated with clozapine is depicted in Table 1. Madhusoodanan et al.[2] reported a case series of seven patients who developed chronic leukocytosis due to clozapine. None of the seven patients had any history of general medical conditions and infection. They opined that increased WBC count might be due to smoking and male gender as possible risk factors for leukocytosis. Polat et al.[9] also reported case of 41-year-old women case of paranoid schizophrenia, treated with clozapine. She had no history of any medical condition except smoking as her one of the risk factors. Liu et al.[10] also reported a case of 51-year-old man with long history of schizoaffective disorder, without any history of medical condition. However, clozapine was discontinued due to patient’s refusal to do weekly WBC count test.

This case suggests that relationship between the use of clozapine and leukocytosis that is directly proportional. It was also observed that the rapid resolution of leukocytosis after the discontinuation of clozapine. Patient’s WBC count and neutrophil count were within normal limit before initiating clozapine. The risk of the WBC count and neutrophil count was consistent with increase clozapine dose, suggesting a dose-dependent effect. When the clozapine dose was tapered down, the counts decreased proportionately. Moreover, the white cell count and neutrophil count came within normal range after the discontinuation of clozapine.

A medical workup to rule out the common cause of leukocytosis is the first step of management. It is also important to rule out possible risk factors to carry leukocytosis like medications such as lithium,
prednisolone, beta agonist, epinephrine, anesthesia, smoking infections and inflammations such as tissue necrosis, burns, arthritis, and trauma. Medical conditions, such as infarction, seizure, splenectomy, hemolytic anemia and malignancy, should also be ruled out.

CONCLUSION

The incidence of leukocytosis associated with clozapine has been reported rarely in the literature. We observed dose-dependent effect, rise of WBC count and neutrophil count was consistent with increase of clozapine dose, the count decreased proportionately and became normal when there was discontinuation of clozapine.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Ghaznavi S, Nakic M, Rao P, Hu J, Brewer JA, Hannestad J, et al. Rechallenging with clozapine following neutropenia: Treatment options for refractory schizophrenia. Am J Psychiatry 2008;165:813-8.
2. Madhusoodanan S, Cuni L, Brenner R, Sajatovic M, Palekar N, Amanbekova D. Chronic leukocytosis associated with clozapine: A case series. J Clin Psychiatry 2007;68:484-8.
3. McCarthy DA, Perry JD, Melsom RD, Dale MM. Leucocytosis induced by exercise. Br Med J (Clin Res Ed) 1987;295:636.
4. Darko DF, Rose J, Gillin JC, Golshan S, Baird SM. Neutrophilia and lymphopenia in major mood disorders. Psychiatry Res 1988;25:243-51.
5. Abramson N, Melton B. Leukocytosis: Basics of clinical assessment. Am Fam Physician 2000;62:2053-60.
6. Parry H, Cohen S, Schlarb JE, Tyrrell DA, Fisher A, Russell MA, et al. Smoking, alcohol consumption, and leukocyte counts. Am J Clin Pathol 1997;107:64-7.
7. Seifritz E, Hemmeter U, Holsboer-Trachsler E, Pöldinger W. Chronic leukocytosis and neutrophilia caused by rehabilitation stress in a clozapine-treated patient. Pharmacopsychiatry 1993;26:99.
8. Fehsel K, Loeffler S, Krieger K, Henning U, Agelink M, Kolb-Bachofen V, et al. Clozapine induces oxidative stress and proapoptotic gene expression in neutrophils of schizophrenic patients. J Clin Psychopharmacol 2005;25:419-26.
9. Polat A, Cakir U, Gunduz N. Leukocytosis after clozapine treatment in a patient with chronic schizophrenia. Arch Neuropsychiatr 2016;53:84-5.
10. Liu F, Mahgoub N, Ferrando S. Leukocytosis associated with clozapine treatment: A case report. Psychosomatics 2011;52:488-91.

Table 1: Nine case report review on leukocytosis with clozapine

| Authors            | Diagnosis     | Clozapine dose (mg/day) | WBC count (mm$^3$) | Concurrent condition | Outcome  |
|--------------------|---------------|-------------------------|-------------------|---------------------|----------|
| Polat et al.       | Paranoid schiz | 450                     | 24,300            | Smoking             | Discontinued |
| Liu et al.         | Paranoid schiz | 400                     | 22,300            | Refusal to WBC test | Discontinued |
| Madhusoodanan et al | Paranoid schiz | 600                     | 17,200            | Smoking             | Continued |
|                    | Schizoaffective | 600                     | 19,100            | Smoking             | Continued |
|                    | Paranoid schiz | 600                     | 19,000            | Smoking             | Discontinued |
|                    | Schizoaffective | 600                     | 13,000            | Smoking             | Continued |
|                    | Paranoid schiz | 600                     | 12,800            | Smoking             | Continued |
|                    | Undifferentiated | 50                      | 12,600            | Smoking             | Continued |
|                    | Paranoid schiz | 450                     | 12,200            | Smoking             | Continued |

WBC: White blood cell