Clozapine-Induced Febrile Neutropenia and Cellulitis

Klozapine Bağlı Febril Nötropeni ve Selülit

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SUMMARY

Clozapine is one of the atypical antipsychotics and is frequently prescribed to patients with treatment-resistant schizophrenia. Agranulocytosis is a major side effect that may lead to death, which limits its use. This is a case report of a patient that developed febrile neutropenia and cellulitis after treatment with clozapine for 20 weeks.

Key words: Cellulitis; clozapine; febrile neutropenia; granulocyte colony-stimulating factor.

ÖZET

Klozapin atipik antipsikotik ilaçlardan biridir ve sıklıkla tedaviye dirençli şizofereni olgularında kullanılmaktadır. Kullanımını sınırlayan en önemli yan etkisi ölümcül olabilen agranülositozdur. Bu yazıda, 100 mg/gün klozapin tedavisinin 20. haftasında nötropenik ateş ve selülit gelişen olgu sunuldu.

Anahtar sözcükler: *Selülit; klozapin; febril nötropeni; granulosit koloni stimüle edici faktör.*

Introduction

Clozapine is one of the atypical antipsychotics and is frequently prescribed to patients with treatment-resistant schizophrenia. The most severe side effect of this medication is agranulocytosis, and the prevalence of developing this condition ranges between 0.7-4.1%.[1,2] Febrile neutropenia attributed to clozapine use occurs in 0.06% of patients.[3] There have been case reports that have demonstrated that atypical antipsychotics other than clozapine may also induce agranulocytosis.[4,5] In this case report, we present a patient that developed febrile neutropenia and cellulitis that was successfully treated 20 weeks after starting clozapine.

Case Report

A 61-year-old male that had been taking 100 mg of clozapine daily for the past 20 weeks presented with complaints of a right leg rash and fever for three days. His past medical history was notable for a diagnosis of schizophrenia when he was approximately 40 years-old. His symptoms of schizophrenia had not been successfully treated with olanzapine, quetiapine, and amisulpride, and so he was started on clozapine. However, he was advised to discontinue the drug once he developed neutropenia 19 weeks into treatment. However, the patient resumed taking the clozapine and developed a fever and a leg rash four days after he was diagnosed with neutropenia. Neither the patient nor his family had a history of blood dyscrasias. On physical examination his temperature was 38.6˚C, his blood pressure was 120/70 mmHg, and his pulse was 78 bpm. His heart and lungs were within normal limits on auscultation. His right leg however was warm to the touch (Figure 1). His laboratory testing revealed a white blood cell (WBC) count of 300/mm^3, neutrophil count of 0/mm^3, platelet (PLT) count of 186,000/mm^3, hemoglobin (Hb) of 11.6 g/dL, glucose of 111 mg/dL, urea

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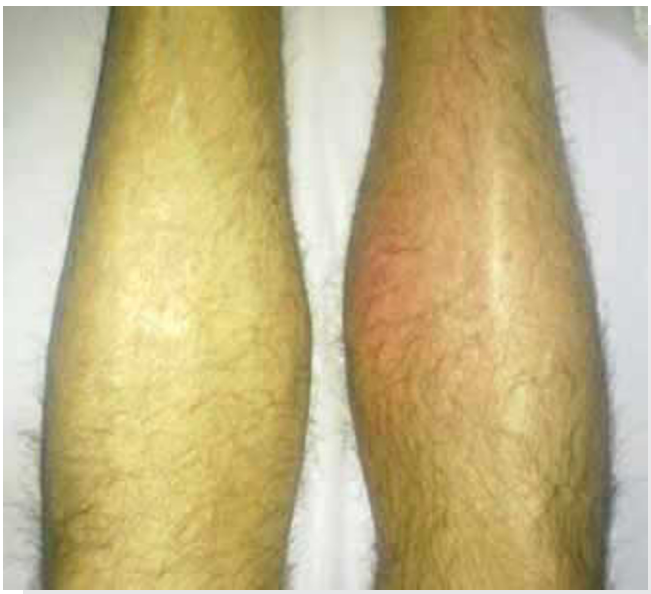

Figure 1. Cellulitis of the right leg.

of 60 mg/dL, creatinine of 1.3 mg/dL, alanine transaminase (ALT) of 13 IU/L, aspartate aminotransferase (AST) of 22 IU/L, Na of 137 mmol/L, K of 4.3 mmol/L, and an albumin of 3.6 g/dL. Atypical cells were not observed on peripheral blood smear.

According to these findings, we diagnosed the patient with febrile neutropenia and cellulitis. Clozapine treatment was immediately stopped and the patient was admitted into contact isolation. His MASCC (Multinational Association for Supportive Care in Cancer) score was 19 and his temperature was 38.6˚C and so blood, throat, and urine cultures were obtained. We began intravenous meropenem at 3 grams/day. Also he was started on subcutaneous granulocyte colony stimulating factor (G-CSF) treatments with Filgrastim at 30 million units/day. All of the cultures were negative for infection. Lower extremity dopplers were performed via ultrasonography and there were no abnormal findings. His fever resolved on the third day of admission and his neutrophil levels began to increase. Meropenem was stopped after 14 days, and his laboratory values were within normal limits on day 14 (Table 1). The patient was referred to the psychiatry clinic so to titrate his antipsychotic medications to treat his schizophrenia.

Discussion

Neutropenia and agranulocytosis resulting from treatment with clozapine usually develops within the first three months of clozapine initiation. In the first 18 weeks of starting clozapine, a total blood count should be performed on a weekly basis. If the blood counts remain within normal limits, then total blood counts may be performed monthly.[1] Despite all of these precautions, agranulocytosis was observed after taking the drug for 11 years in a case report of a patient receiving clozapine treatment.[6] A study conducted with 2,404 patients that had been taking clozapine for 18 weeks reported that 0.9% exhibited neutropenia and 0.7% percent developed agranulocytosis. Yet, all of these patients fully recovered.[1] In another study of 917 patients that were treated with clozapine, it was found that neutropenia occurred in 4.1% of the patients.[2] Between the years of 2005-

Table 1. Laboratory values

Date	WBC (/mm^3) (N=4.600-10.200)	Neutrophil (/mm^3) (N=2.000-6.900)	Hemoglobin (g/dL) (N=12.2-18.1)	Platelet (/mm^3) (N=14.2000-42.4000)
*14.06.2011	7.800	5.100	12.6	241.000
11.10.2011	6.100	3.100	14.2	217.000
18.10.2011	4.200	1.700	14.6	220.000
**25.10.2011	2.100	100	12.2	193.000
***01.11.2011	400	0	11.6	186.000
02.11.2011	500	0	9.6	195.000
04.11.2011	700	0	9.1	195.000
07.11.2011	1.000	200	7.9	224.000
11.11.2011	1.500	300	7.8	321.000
12.11.2011	2.100	600	8.9	362.000
13.11.2011	3.700	1.200	9.3	320.000
14.11.2011	4.800	2.100	8.5	317.000

*Date that clozapine treatment was initiated. **Date that cessation of clozapine was recommended. ***Date of admission to the hospital due to febrile neutropenia with cellulitis.

2009, side effects due to clozapine use occurred in 21,053 patients and 0.006% of them were diagnosed with febrile neutropenia.[3] We diagnosed this patient with neutropenia during the 19th week of treatment. However, his neutropenia worsened due to continuing clozapine against medical advice, and the patient presented with febrile neutropenia and cellulitis.

The pathophysiology of the development of agranulocytosis during clozapine treatment remains unclear. This side effect is not considered to be dose dependent, but it may be the result of an idiosyncratic drug reaction.[7,8] There are case reports in the literature of patients that developed agranulocytosis due to several other antipsychotic medications.[5,6] Clinical trials and case reports have demonstrated that G-CSF is useful in treating clozapine-induced granulocytopenia by stopping agranulocytosis and increasing the number of granulocytes and macrophage precursors in the bone marrow.[1,2,9] In this case report, the patient responded to G-CSF treatment. Because the patient developed neutropenia before the cellulitis was diagnosed, we concluded that the neutropenia developed from being treated with clozapine and that the cellulitis resulted from the neutropenia.

Conclusion

In conclusion, white blood cell counts should be routinely performed in patients who are taking clozapine. It is imperative to detect neutropenia in patients taking atypical antipsychotics early on so to avoid complications such as cellulitis and to guide clinical treatment in case agranulocytosis does develop.

Conflict of Interest

The authors declare that there is no potential conflicts of interest.

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