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Letter to the Editor

Clozapine-induced eosinopenia correlates with high drug serum levels: A case report

Clozapine is the best treatment option for treatment-resistant schizophrenia, yet its use is limited in most clinical settings (Ismail et al., 2019; Mukku et al., 2018) because of the risk of severe, potentially life-threatening side effects including myocarditis, paralytic ileus, agranulocytosis, and the consequent need for a close monitoring (frequent blood draws, periodic visits) (De Berardis et al., 2018; Nielsen et al., 2013). The process leading to clozapine-associate blood dyscrasias such as thrombocytopenia, thrombocytosis, and eosinophilia is still controversial; hypotheses include immunological, genetic or toxic mechanisms, or a multifactorial phenomenon (Dettling et al., 2007).

The metabolism of clozapine presents a wide interindividual variability, likely due to genetic factors, age, gender, concurrent disease, concomitant medications, and smoking (Bersani et al., 2011). Since the magnitude of some side effects might be related to plasma levels (Olesen et al., 1995) therapeutic drug monitoring of clozapine is recommended to reduce the likelihood of adverse events.

Here we describe the case of a 45-year-old Caucasian female with a DSM-IV-TR diagnosis of paranoid schizophrenia, treatment-resistant, who presented an unexpected hematological dyscrasia during clozapine treatment and was investigated through therapeutic drug monitoring.

The patient had developed anorexia nervosa around the age of 20; in the next years there was the onset of auditory hallucinations and erotomanic delusions, and around the age of 27 she was diagnosed with schizophrenia. During the years she presented with complex bizarre delusions focused on electric fields and theft of organs, and often ingested foreign objects according to the delusional thought that these would have fixed her organs. In the patient's history, two severe suicide attempts were reported. She had been on several antipsychotic medications (e.g. haloperidol, olanzapine, risperidone), with poor benefits. Due to persistence of severe psychotic symptoms, clozapine was started on January 2013, during her stay in a therapeutic community located in Northwestern Italy.

The initial daily dosage was 25 mg, gradually raised to 250 mg over two months. Concurrent treatments included delorazepam, escitalopram, sodium valproate, haloperidol, pregabalin (afterwards, these last three medications were gradually tapered and stopped). Clozapine reduced the patient's psychotic symptoms after two months, yet provoking several severe side effects: sedation, dizziness, nausea and vomit. Furthermore, the eosinophil count and percentage, always within the limits before starting clozapine, decreased to zero after one month of treatment and remained zero in the following months (Table 1). All other blood cells were in the normal range.

Serum clozapine level was checked and found 1268 ng/ml, well above the reference interval (350–600 ng/ml). Therefore, clozapine daily dosage was gradually reduced and most of the side effects disappeared; nonetheless, despite dose reduction from 250 mg to 125 mg/d during the following 9 months, clozapine serum concentrations did not significantly decrease and the eosinophil count remained zero (Table 1). Only in January 2014, when a daily dose of 125 mg was reached, clozapine concentration decreased to 801 ng/ml and the eosinophil count slightly started to increase again. Fortunately, during this time frame the reduction of clozapine did not lead to a worsening of psychotic symptoms.

A recent letter to the editor by Jakobsen & Fink-Jensen described chronic eosinopenia in clozapine-treated schizophrenic women (N = 15, 83.3% of the female sample) and men (N = 4, 16.7% of the male sample). As it was unknown whether eosinopenia predated clozapine treatment, the Authors argue about the possibility of a drug-induced blood dyscrasia or of a gender specific difference in schizophrenia pathogenesis (Jakobsen and Fink-Jensen, 2018). Regrettably, no data were reported about patients' clozapine serum levels, which might allow to compare the results described by Jakobsen & Fink-Jensen to ours, since we found that in the case we described eosinopenia was strictly related to high clozapine serum levels.

In another recently published case report, the emergence of eosinopenia under clozapine predated the onset of agranulocytosis, therefore it was suggested as a predictor for a more severe hematological dyscrasia (Yang et al., 2018). Nonetheless, what we observed in our case report did not support the hypothesis by Yang and coworkers, as we did not observe a decrease in absolute or relative neutrophils count, neither during the period of eosinopenia nor in the subsequent period.

The risk of developing neutropenia and agranulocytosis during clozapine administration is approximately 3% and 0.8%, it is higher during the first 6 months of treatment and reduces significantly afterwards (Nooijen et al., 2011). A higher clozapine dosage may lead to a greater number of side effects, yet there is a dearth of data supporting the relationship between dose, plasma levels, and side effects severity (Remington et al., 2013). In our case, the patient showed a total eosinopenia, which started to resolve when clozapine serum concentration lowered to values around 800 ng/ml, suggesting a dose-effect relationship.

While eosinophilia is associated with a wide variety of disorders whose clinical manifestations range from benign asymptomatic presentations to life-threatening complications, including endomyocardial fibrosis and thromboembolism (Klion, 2015), the consequences of eosinopenia are not commonly described. Nevertheless, a recent review highlighted the role of eosinophils not only in defense to parasitic and helminths infections, but also in immunomodulation, and in the host response to viruses, fungi, and bacteria (Ravin and Loy, 2015). For this reason during clozapine treatment a regular check of eosinophil count should be advocated, especially in patients living in underdeveloped countries where parasitic infections and other communicable diseases are widespread, in order to avoid the onset of potentially serious health conditions.

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Table 1
Therapeutic drug monitoring of clozapine and eosinophil count.

Date Month/year	Clozapine (mg/day)	Serum clozapine level (ng/ml)*	Eosinophil count (10^9/l)
01/2013	0		0,14
01/2013	75		0,2
01/2013	125		0,06
02/2013	125		0
02/2013	125		0
02/2013	125		0,01
03/2013	175		0
04/2013	250	1268	0
06/2013	200	1109	0
07/2013	200	1386	0
09/2013	150	1011	0
10/2013	150	1148	0
12/2013	125	1031	0
01/2014	125	801	0,01
06/2014	125	989	0
11/2014	125	764	0.15

* Serum Clozapine reference interval: 50–700 ng/ml.

Ethical approval

Not applicable.

Informed consent

Informed consent was obtained from the patient's legal tutor.

Conflict of interest

The authors declare that they have no conflict of interest.

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