CASE REPORT

Clozapine-induced severe eosinophilia: report of a case with good outcome

Eosinofilia induzida por clozapina: relato de um caso de bom desfecho

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ABSTRACT

Introduction: Clozapine is the antipsychotic of choice in the treatment of refractory schizophrenia. However, its side effects, such as eosinophilia, may preclude its use. **Methods:** Case report and literature review. **Results:** Young woman, 19 years old, diagnosed with hebefrenic schizophrenia, admitted at Unicamp's psychiatry ward after psychotic symptoms relapse. Clozapine was started after unsuccessful attempts with risperidon and olanzapine. By the fourth week of clozapine use, eosinophils began to increase. Drug titration was stopped, but eosinophils counts continued to rise up, reaching the mark of 5200/mm^3. Due to severity of psychotic symptoms and to the good response obtained with clozapine, we decided to investigate organs involvement before withdrawing the medication. As the patient had no organs involvement, clozapine was maintained and one month after eosinophils peak, it was already normalized. **Conclusion:** Eosinophilia should not necessarily lead to clozapine's withdrawal. Patients who present eosinophilia must be at rigorous observation for organs involvement, and if there is no such involvement, clozapine might be maintained, considering the possible benign and transitory nature of the eosinophils count elevation.

Keywords
Clozapine, eosinophilia, refractory schizophrenia.

RESUMO

Introdução: Clozapina é o antipsicótico de escolha no tratamento de esquizofrenia refratária. No entanto, ela apresenta uma série de efeitos colaterais, como a eosinofilia, os quais podem inviabilizar sua continuação. **Métodos:** Relato de caso e revisão da literatura. **Resultados:** Jovem de 19 anos, com diagnóstico de esquizofrenia hebefrênica, internada na enfermaria de psiquiatra do HC-Unicamp por reagudização de sintomas psicóticos. Durante internação, após tentativas frustradas de uso de antipsicóticos como risperidona e olanzapina, iniciou-se clozapina. Na quarta semana após introdução, iniciou-se aumento de eosinófilos. Tendo em vista a gravidade do quadro e a ótima resposta obtida com relação aos sintomas psicóticos, o aumento de dose de clozapina foi interrompido, mas a medicação foi mantida. Mesmo com a dose estabilizada, a eosinofilia continuou a aumentar, chegando a 5.200/mm^3. A paciente foi investigada para lesões de órgãos pela possível inflamação, mas nada foi encontrado. Assim, clozapina foi mantida e, um mês após seu pico, eosinófilos normalizaram-se. **Conclusão:** Eosinofilia não necessariamente impõe a interrupção de clozapina. O paciente deve ser man-

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Palavras-chave
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tido em observação rigorosa em busca de lesões de órgãos. Caso não haja indício de lesões, é justificável manter a clozapina, tendo em vista o possível caráter benigno e transitório da eosinofilia.

INTRODUCTION

Various cohort studies indicate that 20%-30% of patients with schizophrenia meet criteria for refractory schizophrenia[1]. Clozapine is an atypical antipsychotic agent with an established and valuable role in the treatment of these patients. Studies have shown its superiority when compared to other antipsychotics. It has proven to be effective, reducing overall morbidity and suicidality in this population[1,2].

Clozapine is associated with various haematological adverse effects, including leukopenia, neutropenia, agranulocytosis, leukocytosis, anaemia, eosinophilia, thrombocytopenia and thrombocytosis. It is also associated with other serious adverse effects such as thromboembolism, myocarditis, cardiomyopathy, diabetes mellitus, weight gain and seizures. Less serious adverse effects include sedation, drowsiness, tachycardia, constipation and hyper salivation[3].

A number of articles have been published emphasizing the occurrence of eosinophilia in clozapine-treated patients and its consequences[2,4-13]. Nevertheless, none of them reported a case as severe as ours and with such a benign outcome.

CASE REPORT

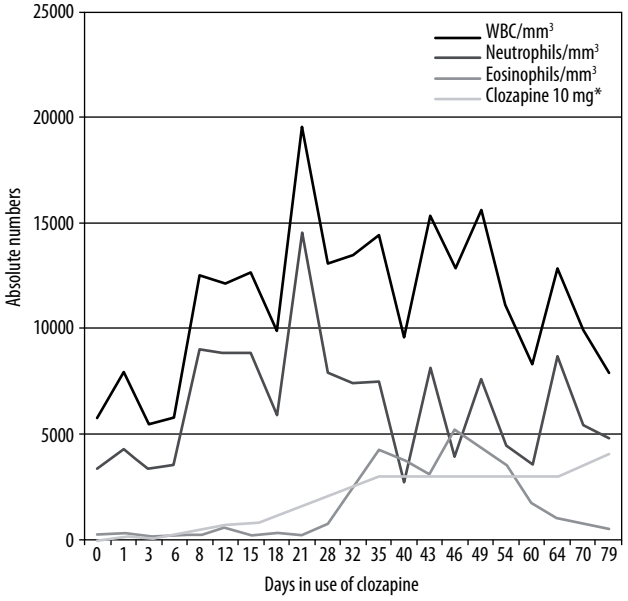
P., female, 19 years old, unemployed, living with parents and younger brother, was admitted at Unicamp's psychiatry ward in July 7th 2011 presenting agitation and disorganized behavior. She presented psychotic symptoms for the first time at the age of fifteen and had no family history of any mental disorder whatsoever. During those four years before being admitted to our service, she has passed through several psychiatrists (mainly after her schizophrenia diagnosis) and treatments including risperidon, quetiapine and carbamazepine. Those last two medications were introduced during a one month hospitalization in another service. According to her family, her psychotic symptoms have been worsening through the years and P was far different from the girl she used to be.

At admission she was using quetiapine 800 mg/day and carbamazepine 600 mg/day. During the first days of hospitalization she also presented: perplexity, depersonification, bizarre and paranoid delusion, social disinhibition, hostility and suicidal thoughts. A differential diagnosis of psychotic mania was considered, but the psychotic features of her clinical presentation were far more pronounced than the mood alterations and since the first episode, four years earlier, she had never returned to her previous functional level. By this time, we considered the diagnosis of hebephrenic schizophrenia, which is our hypothesis until nowadays.

Since she had a history of good response to risperidon, we decided to resume prescribing it. Two weeks later, with 8 mg/d, no response was obtained. Her agitated behavior became a huge problem as mechanical restraint was difficult to be rightly done – she was too thin and always achieved to get off of it – and she was very tolerant to sedation. We were using high doses of antipsychotics and benzodiapines, which calmed her down for only a few moments. Despite our efforts she kept putting herself at risk. She was provocative and aggressive with other patients, her family and the ward team. During this time she was also manipulating her vagina and anus, which frequently provoked bleedings and the necessity of special care. So, we started olanzapine. One month after admission, using risperidon 6 mg/day, olanzapine 30 mg/day, sodium valproate 750 mg/day and clorpromazine 100 mg/day and without any improvement, we decided to start clozapine. The initial CBC was entirely normal and her initial eosinophils count was 310 per mm^3. We started clozapine with 12.5 mg per day, increasing by 25 mg every two days until 100 mg/day was reached. After that, we increased by 50 mg every two days. During titration, we gradually withdrew other antipsychotics she was using.

By the fourth week after clozapine was started, the patient was taking 200 mg per day and her eosinophils count began to increase. One week earlier, the patient presented diarrhea, nausea and colic; symptoms that made us believe that she might be infested by intestinal parasites. We continued clozapine titration, collected all faeces exams (which were negative) and started albendazole. Since the gastrointestinal symptoms continued despite it all, they were attributed to clozapine and it was decided to stop titration and maintain the patient under close observation. By then, she was receiving 300 mg/day of clozapine. Hematologic consultation was solicited. The hematology team also believed the eosinophilia was due to clozapine. They suggested a bone marrow biopsy should be performed if the hematological features did not normalize in a few weeks. Considering symptoms' severity and the lack of response to other antipsychotics, we decided not to withdraw clozapine and maintain the dose she was taking at the moment: 300 mg/d. Colonoscopy and endoscopy, both with biopsy, were performed to look for eosinophilic infiltrate. By that time eosinophlic colitis was one of the hypotheses we considered for the gastrointestinal symptoms. No sign of colitis or infiltrated was seen, but a lesion with traumatic characteristics was observed at her distal rectum. It was attributed to her self-manipulation.

Even after stopping increasing clozapine doses, the eosinophils count reached 5200/mm^3 (Figure 1) and then began to decline until normal counts were reached one month after its peak. Changes in WBC, neutrophils, eosinophils and clozapine doses over time are presented in figure 1. Besides sialorrhea and weight gain, no other side effects were detected. Blood counts remained normal until august 2013, date of her last monthly medical appointment. The patient had a good response to clozapine with complete remission of psychotic and disorganized symptoms.



* The values of clozapine dose have been multiplied by 10 only to be better visualized on the graph.

Figure 1. Clozapine daily dose and blood counts variations.

DISCUSSION

We describe here a case of clozapine use in refractory schizophrenia, with a serious eosinophilia and with no discontinuation of the drug.

Drug-induced eosinophilia is a non-dose-dependent side effect of clozapine[2], whose pathophysiology is still poorly understood. It is thought to be mediated either through a direct toxic effect on the bone marrow or through an immune-mediated reaction. It is also possible that both might co-exist or that other different mechanisms might also be involved[3,5,7,12-14].

The literature on clozapine-induced eosinophilia is relatively scarce. This hematological side effect has been found in 0,2 to 61,7% of clozapine-treated patients[2,4-9,15]. The high variability of the reported rates can be attributed to four factors: small samples sizes, differences in patient pools, varied trial lengths and inconsistencies in the definition of this dyscrasia[8]. This all point to the necessity of more studies on this theme, with bigger samples.

According to Sandoz and Novartis guidelines, clozapine should be withdrawn when eosinophil counts achieve 1400 and 3000/mm^3, respectively[5,7,10]. However, since there is no clear evidence for a distinct disadvantage for a patient with an increasing eosinophil count, an uncritical withdrawal of the drug could deprive a patient of the benefits of clozapine. Therefore, the decision to discontinue treatment should be made for each patient individually[2,5].

Deliliers[4] reported mild eosinophilia (eosinophil > 400/mm^3), unrelated to concomitant pathologies and with no difference between the sexes, in 52 of 2404 patients (2.2%) after a median drug exposure of 27 days. None of these cases required the interruption of clozapine administration, and all spontaneously resolved 3-4 weeks after onset.

Tiihonen and Paanila[10] described a case where clozapine was discontinued at the value of 1500/mm^3 eosinophils, but restarted after normalization. The patient has not presented eosiniphilia ever since.

Stricker and Tielens[11] and Lucht and Rietschel[5] reported cases where clozapine was withdrawn due to eosinophilia and no more attempts of reintroduction were made. Differently, Zipris *et al.*[2] described a case where the medication was discontinued and after normalization of parameters a new titration was started. Unfortunately, there was recurrence of eosinophilia and clozapine had to be interrupted for good.

A few articles report cases where the eosinophilia preceded the occurrence of end-organs inflammation (pancreatitis, hepatitis, colitis, myocarditis and pleural effusion). In those cases, clozapine's withdrawal was mandatory due to the eosinophilia's life threatening consequences[6,9,12,13,16]. Nevertheless, the possibility of its reintroduction exists even in such cases provided that a close clinical monitoring is mantained[13].

Patients presenting moderate to severe eosinophilia should be treated preferentially in a general hospital psychiatric ward, in order to assure proper clinical assessment and support.

CONCLUSION

Eosinophilia is not necessarily a marker for medical illness. Its presence does not obligate clozapine's withdrawal, even when counts are extremely high. Close observation must be maintained monitoring the possibility of end-organs inflammation, but clozapine might be continued. We report a successful example of such situation.

INDIVIDUAL CONTRIBUTIONS

Carla R. B. Marcelino and **Clarissa de R. Dantas** – Were part of the team responsible for the patient's care and also carried out the literature review and the writing of this article.

CONFLICT OF INTERESTS

Carla Regina Bornhofen Marcelino and Clarissa de R. Dantas have no conflict of interests.

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