Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Severe granulocytopenia in a patient on long-term use of clozapine and with COVID-19

Dear Editor,

Three decades after its relaunching, clozapine remains the pharmacological mainstay for treating refractory schizophrenia. Nevertheless, it is still underprescribed mainly because of the fear of its severe adverse effects, especially the hematological ones, such as severe granulocytopenia and agranulocytosis (Wiciński and Węclewicz, 2018; Dragoi et al., 2020).

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in Wuhan, China, and rapidly became a pandemic. Initially thought of as a respiratory disease, it is currently considered an infection that involves multiple systems and may lead to a cytokine storm (Terpos et al., 2020).

The authors describe the case of a patient with schizophrenia, in use of clozapine for 14 years, who developed progressive granulocytopenia that became even more severe with the co-occurrence of COVID-19.

To the best of the authors' knowledge, this is the first report of significant leukopenia in a patient with COVID-19 during clozapine treatment. Besides, it occurred in someone with long-term use of clozapine. Though rare, very late-onset clozapine-induced agranulocytosis is described in the literature, up to 22 years of use (Lahdelma and Appelberg, 2012).

The case: a Caucasian 52-year-old male without any comorbidities was diagnosed with schizophrenia in his early twenties, with an inadequate response to several antipsychotics. In 2007, clozapine was prescribed, with a gradual titration until 500 mg/day, when the positive symptoms remitted. In 2018, there was another dose increase, to 600 mg/day, because mystic religious delusions reemerged.

In April 2017, the full blood count revealed thrombocytopenia with a total platelet count of 130,000/μL, leading to a folic acid 5 mg/day prescription and the normalization of this parameter after six months, achieving 167,000/μL. The patient was also using atenolol 25mg/day, due to tachycardia, since November 2020 and did not use any other medications until May 2021.

His blood counts were rigorously monitored since the beginning of his clozapine treatment with no other alterations than the aforementioned transient thrombocytopenia. Even during the pandemic, they were monthly monitored, remaining at his baseline, similar to his previous hemograms, with the following white cell counts in February 2021: total white blood cell count (WBC)=4,200/μL, absolute neutrophils count (ANC)=3,000/μL, total lymphocytes count (TLC)=1,200/μL. His platelets were around 160,000/μL.

On Mar 3, 2021, he developed mild blood dyscrasia: WBC = 2,500/μL, ANC = 1,981/μL, and TLC = 794/μL. Subsequent full blood counts became normal until Apr 16, when he developed leukopenia, with both neutropenia, lymphopenia, leading to a clozapine prescription reduction to 500 mg/day. As the parameters kept declining, on May 5, the clozapine prescription was further decreased to 400 mg/day, and haloperidol 2,5 mg/day was introduced. On May 12, the counts were: WBC = 1700/μL, ANC = 690/μL, and TLC = 500/μL, and there was another reduction in clozapine dose, to 200 mg/day, together with an increase of haloperidol, to 5 mg/day. Five days later, he developed granulocytopenia, achieving the nadir of WBC = 1,400/μL, ANC = 277/μL, and TLC = 819/μL, which lead to the suspension of clozapine, the increase of haloperidol to 7,5 mg/day, and the execution of an infectious screening. The investigation included the reverse transcription-polymerase chain reaction (RT-PCR) test for Sars-Cov-2, which was positive.

The patient had had brief contact with a COVID-19 diagnosed person seven days earlier and was asymptomatic. Therefore, he was hospitalized in a COVID ward, where both psychiatric and hematological teams were responsible for him, monitoring his vital signs and inflammatory indicators, which remained within normal parameters. Differential diagnosis was made with infectious diseases, with a normal chest x-ray and serological tests for hepatitis B and C, HIV, mononucleosis, and cytomegalovirus, all negatives. Nutritional deficiencies were also considered, with an iron profile and folate levels within normal ranges. There was a B12 count of 166 pg/mL, for which cyanocobalamin was prescribed after discharge.

The patient's white blood cells started to decrease two months before he tested positive for COVID-19, and after the suspension of clozapine, his white cell parameters gradually and steadily normalized, which suggests a possible causal role of clozapine. On May 31, they were: WBC = 3,500/μL, ANC = 2,076/μL, and TLC = 973/μL. The patient remained asymptomatic with normal vital signs and no clinical signs of infections. Until Jun 17, he had no rebound psychotic symptoms after the clozapine suspension. Then, he became persecutory with a family member and had trouble sleeping. Thus, haloperidol was increased to 10 mg/day, and clonazepam 1 mg/day was prescribed, and these symptoms remitted. At any time, the patient did not present respiratory symptoms. Regarding his psychiatric condition, as the patient has refractory schizophrenia, if the current prescription does not provide good outcomes, a future cautious clozapine re-challenge will undoubtedly be considered.

The effects of COVID-19 on patients using clozapine are not well established (Rendon-Quintero et al., 2021). The Sars-Cov-2 enters the cell after binding to the angiotensin-converting enzyme 2 (ACE2) receptors, found in the lymphocyte's membrane, leading to apoptosis. Besides, a cytokine storm can also lead to apoptosis, so lymphopenia is well established and related to more severe cases, like those with thrombocytopenia and leukopenia. Also, acute respiratory distress syndrome (ARDS) is related to neutrophilia, and data on neutropenia are sparse (Terpos et al., 2020).

Patients with schizophrenia may be more susceptible to COVID-19

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due to poor self-care, raised risk of pneumonia, and comorbidities. However, an outbreak in a Colombian psychiatric clinic shows that many patients could remain asymptomatic (Rendon-Quintero et al., 2021) like the patient described above.

To conclude, in the case presented here is unwarranted to pinpoint the causal role played by clozapine or COVID-19, either isolated or in combination, in the genesis of the severe granulocytopenia. However, we think the unique (as far as we know) circumstances of our case and the good outcome of a potentially serious complication makes it worth reporting, as it may contribute to enlarge the database to inform the management of these complications in the world after the pandemic.

Declaration of Competing Interest

The authors have no potential competing or conflicting interests to report.

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