

# Two Patients with Schizophrenia Treated with Clozapine Developed Neutropenia After Receiving a COVID-19 Vaccine

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**Background:** We observed two cases of patients with schizophrenia who were treated with clozapine (250mg/day and 275mg/day, respectively) and showed neutropenia after receiving a COVID-19 vaccine (BNT162b2).

**Case Presentation:** Case 1 is a twenty-two year old woman with a diagnosis of schizophrenia. She enrolled in Clozaril® Patient Monitoring Service in 2017 and had been taking clozapine for 4 years. She received two doses of a COVID-19 vaccine and developed neutropenia ( $1850/\text{mm}^3$  (37.9% of white blood cell  $4880/\text{mm}^3$ )) 6 days after the second vaccination, but her neutropenia self-resolved naturally. Case 2 is a twenty year old woman with a diagnosis of schizophrenia. She enrolled in Clozaril® Patient Monitoring Service in 2020 and had been taking clozapine for 10 months. She received two doses of a COVID-19 vaccine and white blood cell and neutrocyte counts were below ( $3730/\text{mm}^3$  and  $1440/\text{mm}^3$  (38.6%), respectively) the lower limits 3 days after the second vaccination. She had to discontinue clozapine according to the withdrawal definition (her neutrocyte count was  $<1500/\text{mm}^3$ ), and her neutropenia self-resolved naturally.

**Conclusion:** Physicians need to have a strict follow-up protocol in place for patients after vaccination for COVID-19.

**Keywords:** clozapine, COVID-19, vaccine, neutropenia

## Introduction

Clozapine is used to treat treatment-resistant schizophrenia in patients in Japan and worldwide and is effective against the major symptoms of schizophrenia: hallucinations, delusions, and cognitive impairment.<sup>1,2</sup> Therefore, clozapine is a very important drug in clinical psychiatry, but clozapine can cause severe adverse events.<sup>2-4</sup>

Neutropenia is a severe adverse event, so psychiatrists need to frequently monitor the neutrocyte counts of patients taking this medication. In Japan, every time psychiatrists prescribe clozapine, psychiatrists must report the neutrocyte data of all of the patients taking clozapine to monitor and prevent neutropenia, and psychiatrists must report these data to the Clozaril Patient Monitoring Service (CPMS) by The Expert Committee for Clozaril Patient Monitoring Service via the internet. In the Japanese definition, leukopenia and neutropenia were defined as counts  $<4000/\text{mm}^3$  and  $<2000/\text{mm}^3$ , respectively. If a patient has a white blood cell count or a neutrocyte count that is under the limit, the patients must have their blood examinations monitored more frequently, or psychiatrists have to stop prescribing the clozapine.

Recently, we have been affected by the COVID-19 pandemic and have been trying to prevent COVID-19 infections, and patients with schizophrenia taking clozapine have been recently vaccinated. Although many vaccinations were known to might induce neutropenia,<sup>5</sup> we have seen two patients with schizophrenia taking clozapine who developed neutropenia after a COVID-19 vaccination (BNT162b2), and we report the cases here. Written informed consent was obtained from the patients for the publication of this case report. The study was approved by the Ethics Committee of the Hirosaki University Hospital.

## Case Presentations

### Case 1

Case 1 is a twenty-two year old woman. She had experienced visual hallucinations and persecutory delusions for 9 years. After taking the usual pharmacotherapy, including risperidone and aripiprazole, she started taking clozapine 4 years prior to this report.

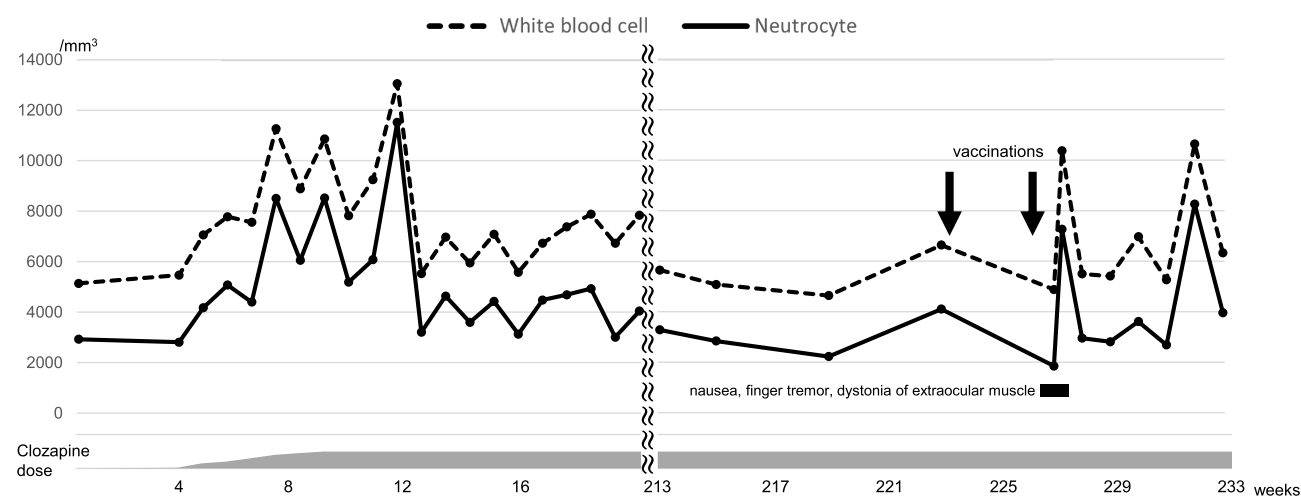
She experienced mild side effects, including hypersalivation, constipation, and hypersomnia, but her symptoms eventually improved. Her white blood cell and neutrocyte counts were over the lower limits ( $4000/\text{mm}^3$  and  $2000/\text{mm}^3$ , respectively), so the physicians maintained the same prescription of clozapine at the same dosage (250 mg/day). In addition to clozapine, she had taken small dose of paroxetine, trihexyphenidyl, levocetirizine, lithium carbonate, bromazepam, midodrine, domperidone, shakuyakukanzoto and sennoside to treat depressive mood, probable drug-induced parkinsonism, allergy, mood instability, anxiety, dizziness, nausea, muscle cramps and constipation, respectively, but the dose and usage did not change much before the episode shown below. Physician had confirmed that she complied with the medication.

She had two doses of a COVID-19 vaccine while taking clozapine. She visited the hospital and underwent a blood examination 6 days after the second vaccination. Suddenly, her neutrocyte counts were below ( $1850/\text{mm}^3$ , (37.9% of white blood cell  $4880/\text{mm}^3$ )) the lower limits, so she had to undergo frequent blood examinations. In addition, she experienced nausea, finger tremor, and dystonia of the extraocular muscles a few days after the second vaccination. After that, her laboratory data and symptoms improved naturally in two days and one week, respectively (Figure 1).

### Case 2

Case 2 is a twenty year old woman. She had experienced visual hallucinations and invasive delusions for 5 years. After taking the usual pharmacotherapy with risperidone and aripiprazole, she started taking clozapine 10 months prior to this report.

After starting clozapine, her creatinine kinase became elevated ( $\sim 1600$  IU/L) for a while but naturally decreased to the normal limit. She experienced mild side effects, including hypersomnia and hypersalivation, but her symptoms improved. Her white blood cell and neutrocyte counts were over the lower limits ( $4000/\text{mm}^3$  and  $2000/\text{mm}^3$ ), so the physician continued her prescription of clozapine at the same dosage (275 mg/day). In addition to clozapine, she had taken small dose of domperidone, lemborexant and flunitrazepam and ramelteon, biperiden, lithium carbonate and sodium valproate, rupatadine to treat nausea, insomnia, mood instability, allergy, respectively, but the dose and usage did not change much before the episode shown below. Physician had confirmed that she complied with the medication.



**Figure 1** Time course and the data of white blood cell and neutrocyte of case 1.

She had two doses of a COVID-19 vaccine while taking clozapine. She visited the hospital and underwent a blood examination 3 days after the second vaccination. Suddenly, her white blood cell and neutrocyte counts were below ( $3730/\text{mm}^3$  and  $1440/\text{mm}^3$ , respectively) the lower limits, so she had to undergo frequent blood examinations and had to temporarily discontinue clozapine. She did not experience nausea, finger tremor, or dystonia of the extraocular muscles after the second vaccination that the patient in case 1 experienced. After that, her laboratory data improved naturally in one day (Figure 2).

The scores of adverse drug reaction scale of case 1 and case 2 were 5 and 6, respectively and both cases were assessed probable adverse drug reaction,<sup>6</sup>(Supplemental Table 1).

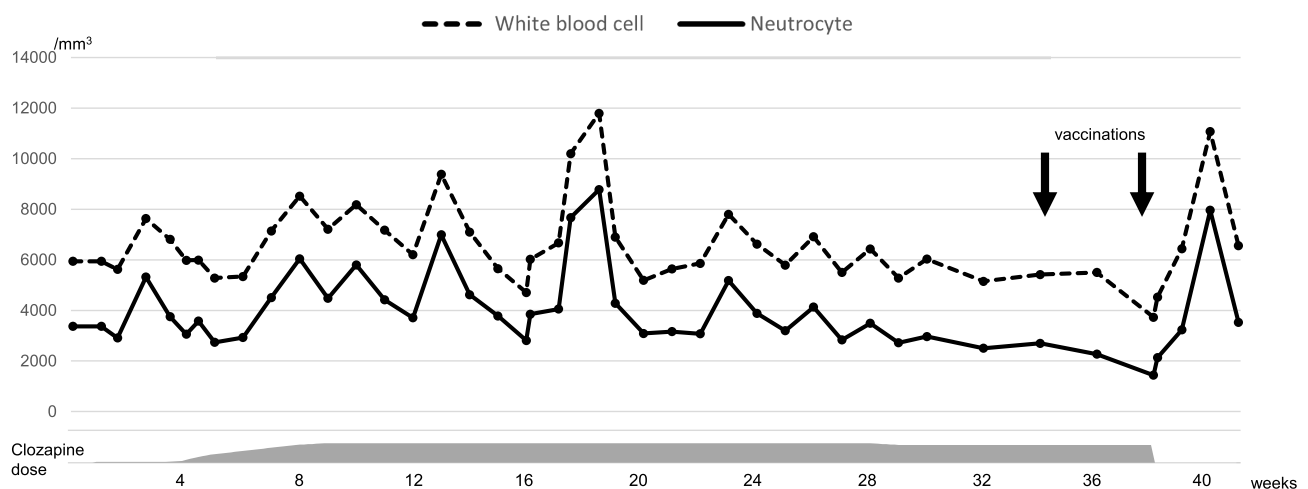
## Discussion and Conclusions

We experienced and reported two cases of patients with schizophrenia who were taking clozapine and who developed neutropenia after vaccination for COVID-19. The patient in case 2 stopped taking clozapine according to the clozapine manual in Japan. After that, her symptoms worsened, and the physicians then tried to restart her clozapine by trying to meet the requirements.

Some reports have suggested that vaccination for COVID-19 might influence clozapine metabolism, the serum concentration of clozapine, the immune response or neutrocyte counts.<sup>7-9</sup> Thompson et al reported a case of a patient who developed an elevation in the clozapine concentration after vaccination, and Niels et al reported an association between an elevated clozapine concentration and neutropenia.<sup>10,11</sup> In particular, the patient in case 1 showed nausea which were thought to be side effects from an elevated clozapine concentration, so this patient's neutropenia might be caused by vaccination and elevated clozapine concentrations secondary to vaccination. Neutropenia caused by clozapine might be associated with the patient's genetic characteristics, but the brother of the patient in case 1, who also took clozapine, did not develop neutropenia after vaccination, so genetic factors might not have influenced the clinical course and the development of neutropenia in the patient in case 1.<sup>12</sup>

Neutropenia naturally resolved in both patients. However, the patient in case 2 stopped taking clozapine, her symptoms worsened, and both of the patients had to frequently go to the hospital to have blood examinations. If these patients need to receive a third vaccination for COVID-19, they should consider having the vaccination as soon as possible after a blood examination to give the patients as much time as possible to recover before the next blood examination. The neutropenias in these patients were mild, so it may be better to avoid having blood examinations during periods of possible neutropenia.

In these cases, there were some limitations. First, we did not evaluate the clozapine concentrations in the two patients; therefore, we could not clarify whether elevated clozapine concentrations might cause neutropenia or whether vaccination might directly cause neutropenia. Second, we could not determine why other patients who were taking clozapine did not develop neutropenia, but they might show neutropenia if they had more frequent blood exams.



**Figure 2** Time course and the data of white blood cell and neutrocyte of case 2.

Patients taking clozapine and having a COVID-19 vaccination might develop neutropenia, so physicians need to develop a strict follow-up plan for them. We could not suggest that concomitant with clozapine treatment and COVID-19 vaccines are contraindicated from the case report, so COVID-19 vaccination should be encouraged in patients prescribing clozapine as well as patients.

## Abbreviation

CPMS, Clozaril<sup>®</sup> Patient Monitoring Service.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Hirosaki University Hospital.

Informed consent was obtained from the patients for the publication of this case report.

## Consent for Publication

Written informed consent was obtained from the patients for the publication of this case report.

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We are appreciated to the patients of the cases.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no financial interests or potential conflicts of interest.

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