Received: 4 July 2022 | Revised: 20 July 2022 | Accepted: 25 July 2022

DOI: 10.1002/pcn5.38

CASE REPORT

PCN Reports
Psychiatry and Clinical Neurosciences
Open Access

Successful rechallenge with clozapine after discontinuation due to drug-induced pneumonia: A case report

Yuki Kikuchi MD[1] | Hiroshi Komatsu MD, PhD[2] | Atsushi Sakuma MD, PhD[2] | Hiroaki Tanifuji B.Pharm[3] | Hiroaki Tomita MD, PhD[4]

[1]Department of Psychiatry, Kodama Hospital, Ishinomaki, Miyagi, Japan

[2]Department of Psychiatry, Tohoku University Hospital, Sendai, Miyagi, Japan

[3]Department of Pharmacy, Kodama Hosipital, Ishinomaki, Miyagi, Japan

[4]Department of Psychiatry, Graduate School of Medicine, Tohoku University, Sendai, Miyagi, Japan

Correspondence
Yuki Kikuchi, MD, Kodama Hospital, 2-5-7 Yamashitacho, Ishinomaki-shi, Miyagi-ken 986-0873, Japan.
Email: ykikuchi@sand.ocn.ne.jp

Abstract

Background: There have been a limited number of case reports of clozapine-induced pneumonia. Few have reported rechallenging of clozapine after discontinuation due to the side-effect.

Case Presentation: A 43-year-old man was diagnosed with schizophrenia after developing auditory hallucinations and delusions of persecution and reference. After diagnosing him with treatment-resistant schizophrenia, clozapine was started. From a starting dose of 12.5 mg/day, we increased it by 25 mg every 2–3 days to reach 150 mg/day by Day 15. On Day 17, his body temperature suddenly rose to 39.6°C (103.3°F) without any other apparent physical symptoms. Blood biochemistry testing showed elevated C-reactive protein (CRP) and high counts of leukocytes and neutrophils, but not eosinophils. Chest computed tomography revealed ground-glass opacities in the lower lobes of both lungs. Suspecting bacterial pneumonia, we started him on levofloxacin 500 mg/day. However, pneumonia exacerbated, and eosinophilia became apparent 5 days after the onset of fever. We suspected acute eosinophilic pneumonia induced by clozapine and discontinued its administration the same day. The patient clinically recovered the next day after stopping clozapine. After stopping clozapine, his psychiatric symptoms, such as persecutory/referential delusions, irritability, and polydipsia, became worse. We decided to rechallenge with clozapine in incremental doses slower than the standard protocol, along with careful monitoring of CRP and eosinophil counts. Pneumonia has not recurred, and his psychiatric symptoms have been well managed.

Conclusion: Our experience suggests that some patients with inflammatory reactions to clozapine can still take the drug if it is reintroduced with caution.

KEYWORDS

adverse effects, clozapine, pneumonia, rechallenge, schizophrenia

BACKGROUND

Clozapine is known to produce a variety of side-effects. Neutropenia and agranulocytosis are two well-known and important ones; three adverse reactions frequently seen at the start of treatment are fever, C-reactive protein (CRP) elevation, and eosinophilia.[1] While such reactions can resolve naturally, clinicians must stay vigilant because they can sometimes progress to potentially fatal complications, such as pneumonia, myocarditis, pancreatitis, and agranocytosis.[1,2]

We recently stopped administering clozapine to a psychiatric patient due to acute eosinophilic pneumonia (AEP) suspected to be induced by the drug. By slower dose escalation with careful monitoring of his blood biomarkers, we were able to reintroduce clozapine into his medication regimen without triggering pneumonia recurrence. To the best of our knowledge, this is the first case of clozapine-induced pneumonia who was eventually able to resume taking the drug without provoking its recurrence.

CASE PRESENTATION

Our patient was a 43-year-old man without any allergies. He had no history other than schizophrenia, including asthma, and his only current physical complication was constipation. He used to smoke 20 cigarettes a day for about 20 years but quit after being admitted to our care. Twenty years ago, he was diagnosed with schizophrenia after developing auditory hallucinations and delusions of persecution and reference. Several antipsychotic drugs, such as risperidone and olanzapine, were administered but did not prevent repeated hospitalizations during psychiatric episodes. Six years ago, while living at home and socially withdrawn, he was institutionalized at our hospital for medical care and protection after repeatedly calling for an ambulance because of persecutory delusions. We prescribed several antipsychotics, but they did not produce sufficient improvements in auditory hallucinations, persecutory delusions, irritability, or disordered thinking, so he has continued to stay in our care for an extended period. Last year, after diagnosing him with treatment-resistant schizophrenia, clozapine was started (Figure 1). He was already taking

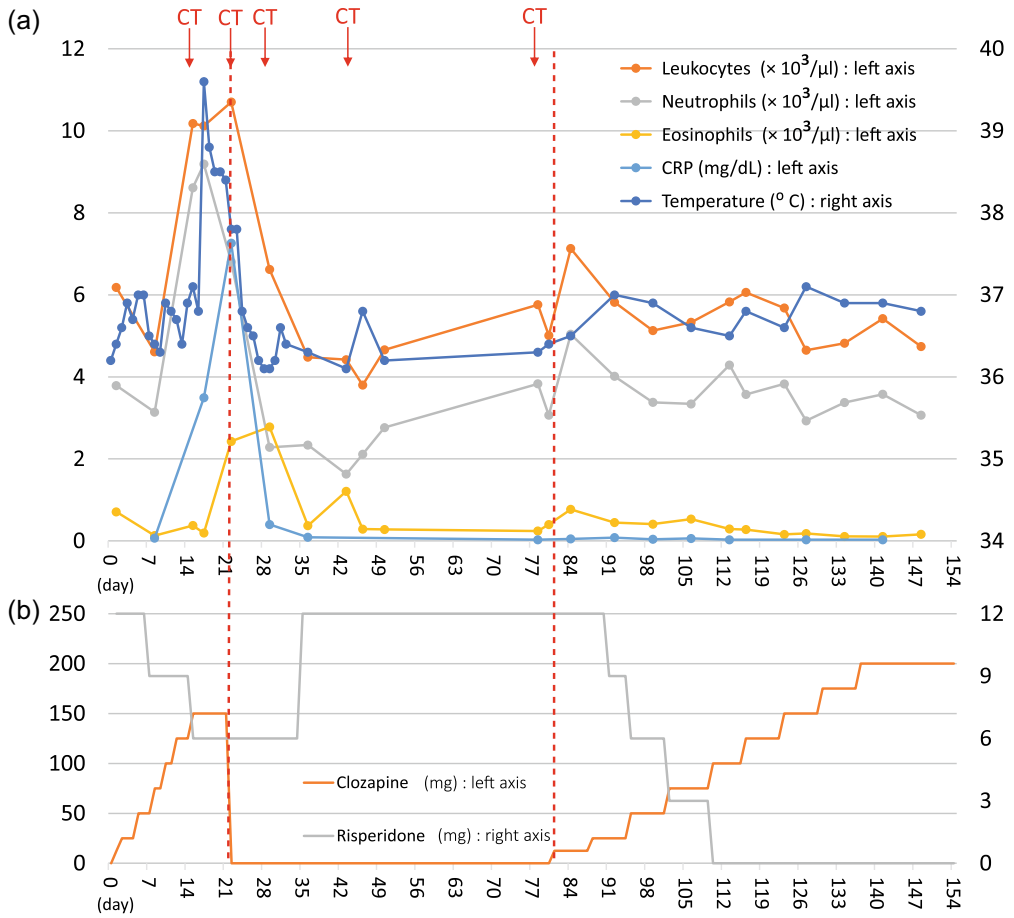

FIGURE 1 (a) Timelines of various biomarkers after starting clozapine. Arrows indicate the time points of the computed tomography (CT) scans presented in Figure 3. The patient's fever was first noted on Day 17. Eosinophilia was seen on Day 22; clozapine was discontinued later that day. His body temperature, white blood cell counts, and C-reactive protein (CRP) level returned to their normal ranges in the days and weeks after that. Clozapine rechallenge started on Day 81. (b) Medication timelines for clozapine and risperidone doses.

risperidone at 12 mg/day, biperiden at 6 mg/day, magnesium oxide at 990 mg/day, and sennoside at 24 mg/day. From a starting dose of 12.5 mg/day, we increased it by 25 mg every 2–3 days to reach 150 mg/day by Day 15, following the protocol issued by the Expert Committee for Clozaril Patient Monitoring Service in Japan. As the dosage increased, no hypersalivation (drooling) or apparent aspiration was observed. On Day 17, the body temperature suddenly rose to 39.6°C (103.3°F) without any other apparent physical symptoms: blood pressure: 99/66 mmHg, heart rate: 106 bpm, breathing rate: 18/min, SpO_2: 98% (Figure 2). Blood biochemistry testing showed elevated CRP (3.49 mg/dl) and high counts of leukocytes (WBC: 10,120/μl) and neutrophils (9188/μl; 91% WBC) but not eosinophils (192/μl; 1.9% WBC). Creatine kinase and amylase levels were within the normal range. The results of urinalysis, (urine) sediment analysis and electrocardiogram were all normal. Chest computed tomography (CT) revealed ground-glass opacities (GGOs) in the lower lobes of both lungs (Figure 3a). Suspecting bacterial pneumonia, we started him on levofloxacin 500 mg/day. The patient's respiratory status and SpO_2 levels did not deteriorate after that (No hypoxia was observed throughout the entire course of the case.): the only persistent symptom was intermittent fever. On Day 22, a blood test showed signs of worsened inflammation (CRP: 7.26 mg/dl) and eosinophilia (2428/μl; 22.7% WBC). Chest CT on the same day showed signs that pneumonia had worsened, along with small volumes of pleural effusion in both lungs and pericardial effusion (Figure 3b). His procalcitonin level (0.1 ng/mL) was within the normal range; a coronavirus PCR test was negative. Pneumonia exacerbated despite the antibiotic treatment, and eosinophilia (2428/μl, 22.7% WBC) became apparent 5 days after the onset of fever. We suspected AEP induced by clozapine and decided to discontinue its administration the same day. By the next day, his fever had dropped below 37°C. By Day 29, his leukocyte and CRP values had improved to within normal ranges, but his eosinophil count remained stubbornly high (2780/μl, 42% WBC). The GGO shadows in both lungs were fainter in chest CT images taken the same day (Figure 3c). Because his psychiatric symptoms had become worse since stopping clozapine, on Day 34, we increased his risperidone dose to 12 mg/day. On Day 43, the patient's eosinophil count was still abnormally high (1211/μl, 27.4% WBC). Chest CT showed marked improvements in the shadows described above but revealed a small, different nodule to have formed in the right middle lobe (Figure 3d). Subsequently, we started to consider clozapine rechallenge as he showed further deterioration in psychiatric symptoms—for example, shouting out in response to other patients' voices—and also developed excessive thirst (polydipsia). Chest CT on Day 78 confirmed that all shadows had disappeared. A blood test showed leukocyte, eosinophil, and CRP values to be within normal ranges, but sodium was low (Na: 113 mEq/L). We attributed this hyponatremia to water toxicity caused by excessive thirst and drinking, as supported by the parallel 10 kg increase in body weight. At this point, we decided to try to rechallenge with clozapine to improve the patient's persecutory/referential delusions, irritability, and polydipsia. Consent to the rechallenge of clozapine was obtained from the patient and a guardian after a shared decision-making process considering the benefits and risks of the treatment. When planning, we referenced a case report in which a patient was successfully rechallenged with clozapine after experiencing clozapine-induced myocarditis.[3] From a starting dose of 12.5 mg on Day 81, we carefully incremented the dose by 25 mg/week, which was slower than the standard protocol. Blood tests were performed parallel to ensure his CRP and eosinophil values stayed within normal limits. Clozapine was ultimately escalated to 200 mg/day, which improved the patient's polydipsia and irritability. Pneumonia has not recurred, and his psychiatric symptoms have been well managed at a dosage of 200 mg/day.

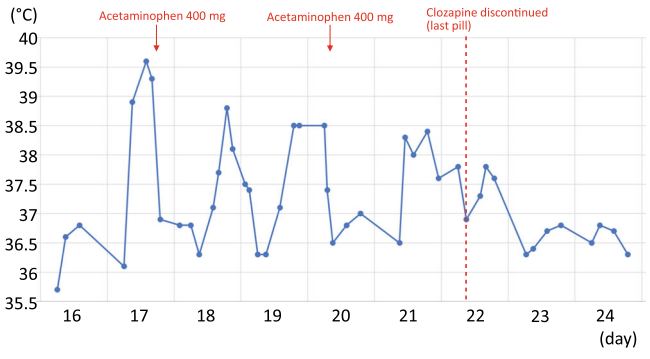

FIGURE 2 Body temperature in the days after fever onset. The patient's fever continued to flare up intermittently after first developing on Day 17. Arrows indicate time points of acetaminophen doses. His fever dropped below 37°C shortly after clozapine was discontinued on Day 22.

DISCUSSION

Recent studies have identified pneumonia as a leading cause of death among patients taking clozapine.[4] This complication is believed to be modulated by a complex interplay of the drug's physiological effects, such as excess saliva secretion, reduced swallowing ability, and sedation.[5] Yet, the direct cause of clozapine-induced pneumonia, as seemed to occur in the present case, remains poorly understood.

Few accounts of clozapine-induced pneumonia have been published: to the best of our knowledge, only nine case reports[6–14] and one case series.[15] In these collected reports, non-specific symptoms suggestive of infection, such as fever and tachycardia, developed shortly (i.e., within the first month) after patients started taking clozapine.[6,14] Ground-glass shadows tend to appear in both lungs on chest X-rays and CT scans and can even migrate.[13,15] Eosinophilia is not consistently present.[6] Some reports also noted how their patients' clinical symptoms rapidly improved after stopping the drug. Rechallenge of clozapine caused pneumonia to recur in several of these cases: the drug was ultimately abandoned in one case,[14] but some reports described the continuation of clozapine administration even after the recurrence of pneumonia.[13,15]

Our patient developed clozapine-induced AEP on Day 17 of the course described here. “Definite” AEP is diagnosed by the presence of four findings according to the modified Philit criteria: (1) acute respiratory illness of less than or equal to 1-month duration; (2) pulmonary infiltrates on chest X-ray or CT; (3) greater than 25% eosinophils in bronchoalveolar lavage (BAL) fluid or biopsied lung

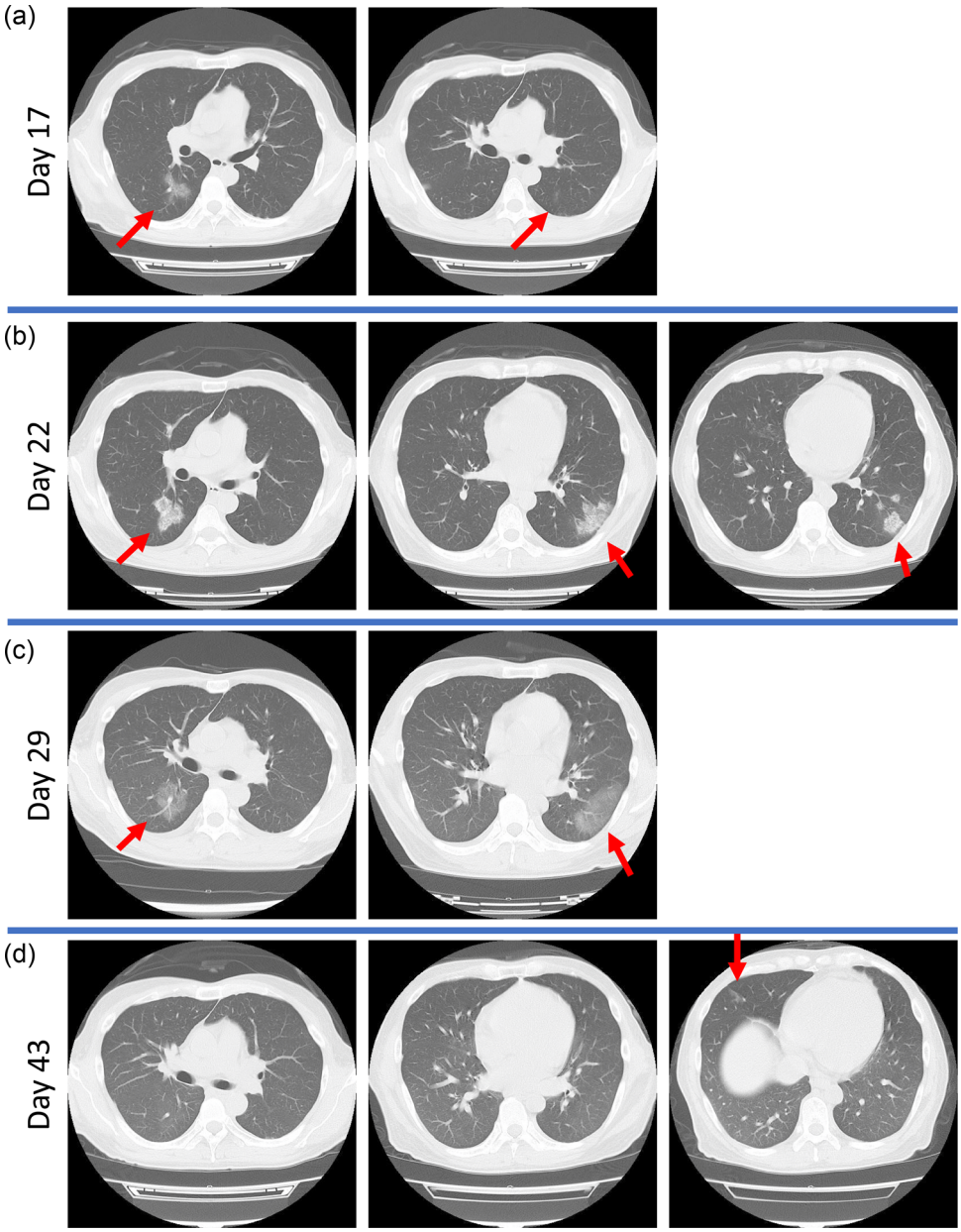

FIGURE 3 Selected chest computed tomography (CT) images. (a) Bilateral ground-glass shadowing was observed in the lower lung fields on Day 17 (red arrows), the same day the fever developed. (b) Clozapine was discontinued on Day 22, prompted by the apparent worsening of these shadows on CT images taken that day. (c, d) The shadows naturally improved in the days and weeks after that.

tissue; and (4) exclusion of other specific pulmonary eosinophilic diseases.[16] Because we did not perform BAL or lung biopsy due to the severe psychotic conditions, our diagnosis is not conclusive per se. However, the dynamics of eosinophil count in peripheral blood in the present case followed a pattern typical of AEP: that is, within normal limits in the acute phase and then increased after a delay of a week or so.[17] This similarity, combined with the fact that our patient's symptoms rapidly improved within a month of clozapine cessation and the CT findings of bilateral GGOs, makes AEP a highly plausible diagnosis. Other causes of AEP include smoking, inhalation of any substance (dust, marijuana, etc.), drugs other than clozapine (including risperidone), parasitic infection, fungal infection, and viral infection (HIV, influenza virus). However, bacterial infections rarely cause AEP.[17] We further excluded bacterial pneumonia for three reasons: (1) the patient's symptoms worsened during the 4 days of levofloxacin administration; (2) procalcitonin, which is suggestive of bacterial infection, was negative; and (3) pneumonia resolved spontaneously and rapidly after clozapine was discontinued. Although sputum culture should have been done prior to administration of levofloxacin, sputum could not be collected due to lack of expectoration. Parasitic and fungal infections were excluded because they are usually caused by contact with food or animals during international travel and are unlikely to occur in the environment during long-term hospitalization (dust and other environmental

factors did not change). Pulmonary aspergillosis is also a condition that occurs in patients with impaired immune function or a history of asthma or cystic fibrosis. In this case, neither the imaging findings (such as bronchiectasis) nor the course of the disease was typical for pulmonary aspergillosis. Influenza virus infection was rarely seen in Japan then, and it is unlikely that the patient contracted it during the strict hospitalization environment for COVID-19 control. Since there were no newly added drugs other than clozapine, other drugs were not likely to cause pneumonia in this case.

We suspected a possible complication of myocarditis and carefully followed up, as the CT showed a small amount of pericardial effusion. In this case, no further signs of myocarditis became apparent. There were no clinical symptoms, such as heart failure or chest pain. Moreover, the ECG and creatine kinase were in the normal range. Troponin was not measured, while it should have been useful in differentiating myocarditis.

The pathological mechanism of clozapine-induced pneumonia is unclear. Some have hypothesized the acute allergic response to be involved.[6,7,15] Although the mechanism of drug hypersensitivity has not been fully elucidated, it is thought to be achieved by reducing the mast cell and basophil response or increasing drug-specific Treg cells. Slow titrations have been recommended as desensitization protocols to avoid such hypersensitivity caused by various drugs.[18] Jose de Leon and colleagues analogize to lamotrigine-induced Stevens–Johnson syndrome, postulating that rapid incrementing clozapine leads to fever, CRP elevation, and potentially severe inflammatory reactions, such as clozapine-induced myocarditis.[19] They propose following a cautious dose-escalation schedule when first starting a patient on clozapine for this reason and being especially cautious when treating Asian patients, overweight patients, poor clozapine metabolizers, or people taking valproate or oral contraceptives (specifically, they recommend incrementing slowly from a starting dose of 6.25 mg, aiming for 75–150 mg/day after 4 weeks while monitoring tolerability, white blood cell populations, and CRP levels).[20]

Cytokines such as IL-6 were not measured, as CRP is often used as a biomarker for re-administration. However, there are reports that clozapine affected blood levels of inflammatory cytokines[21–23] and that IL-6 was elevated in clozapine-induced fever.[24–26] Further research on the relationship between the immunomodulatory effects of clozapine and adverse effects is warranted.

Exploring previous case reports describing instances of clozapine rechallenge, Manu and colleagues found that while rechallenge was a rational option for patients with neutropenia or neuroleptic malignant syndrome, it carried major risks for patients with agranulocytosis or myocarditis.[27] Still, there are a few reports of clozapine-induced myocarditis in which clozapine was successfully resumed (after temporary discontinuation) by increasing the dosage more cautiously while measuring CRP and troponin levels in close coordination with cardiologists.[28–30]

Our dose-escalation schedule followed the instructions issued by the Expert Committee for Clozaril Patient Monitoring Service in Japan. Our patient developed clozapine-induced pneumonia on Day 17 of administration when his dose was 150 mg. This pace was faster than the schedule recommended by Leon et al. for Asian adults of average metabolism: that is, from a starting dose of 12.5 mg, aim to reach 150 mg in 3 weeks and titrate between 175 and 300 mg after 4 weeks.[20] Pneumonia did not recur when we reintroduced clozapine at the slower escalation pace. We consider the following three conditions necessary for re-administration: absence of clinical symptoms, such as fever, cough, and decreased SpO_2; improvement of pneumonia confirmed by CT; and biomarkers of CRP and eosinophil count in the normal range.

The previous case report[14] of failed clozapine re-administration had shown a rapid pace of initial clozapine dose escalation, with the patient developing pneumonia when the dose reached 250 mg/day on Day 11. Vital signs improved 24 h after clozapine discontinuation, and the patient reportedly resumed clozapine at 200 mg/day, suggesting that the lack of slower re-dosing was the cause of the relapse. The reports of multiple recurrences of clozapine-induced pneumonia that could be continued without discontinuation[13,15] cannot be compared to the present case because there are no detailed clinical course or clozapine dose adjustments described in the case reports.

As individuals differ in their metabolism of clozapine, its concentration in blood should be continually monitored. The recommended therapeutic range is 350–600 ng/mL, with a greater risk of side-effects at greater concentrations.[31,32] Leon et al. recommend measuring its blood concentration every week when first starting a patient on clozapine and when escalating dosage.[20] Clozapine blood assays have been covered once a month by medical insurance in Japan since April 2022. However, monitoring clozapine concentration has not become commonly applied to date. Dissemination of clozapine concentration testing may help ensure the safe administration of clozapine.

CONCLUSION

In this case, we avoided pneumonia recurrence by carefully escalating the dosage while monitoring blood biomarkers such as CRP and leukocyte/eosinophil counts. Our experience suggests that some patients with inflammatory reactions to clozapine can still take the drug—after a temporary recovery period—if it is reintroduced with caution and care.

AUTHOR CONTRIBUTIONS

Yuki Kikuchi treated the patient and drafted the manuscript. All authors participated in discussing, writing the manuscript, and approved the final manuscript.

ACKNOWLEDGMENT

We would like to thank Editage (www.editage.com) for English-language editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed for the present study.

PATIENT CONSENT STATEMENT

Written consent to submit this case report for publication was obtained from the patient.

ORCID

Yuki Kikuchi http://orcid.org/0000-0002-1184-8918

REFERENCES

1. Nielsen J, Correll CU, Manu P, Kane JM. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J Clin Psychiatry. 2013;74(6):603–13.
2. Verdoux H, Quiles C, de Leon J. Clinical determinants of fever in clozapine users and implications for treatment management: a narrative review. Schizophr Res. 2019;211:1–9.
3. Hosseini SA, Skrzypcak B, Yasaei R, Abdijadid S, Joolhar F, Win TT, et al. Successful clozapine re-challenge after suspected clozapine-induced myocarditis. Am J Case Rep. 2020;21:e926507.
4. de Leon J, Ruan CJ, Schoretsanitis G, De Las Cuevas C. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother Psychosom. 2020;89(4):200–14.
5. Schoretsanitis G, Ruan CJ, Rohde C, Verdoux H, De Las Cuevas C, Spina E, et al. An update on the complex relationship between clozapine and pneumonia. Expert Rev Clin Pharmacol. 2021;14(2):145–9.
6. Can KC, Karnak D, devrImcI Özgüven H. A very rare adverse effect of clozapine, clozapine-induced interstitial lung disease: case report and literature review. Arch. Neuropsychiatry. 2019;56:313–5.
7. Benning TB. Clozapine-induced extrinsic allergic alveolitis. Br J Psychiatry. 1998;173:440–1.
8. Arias SA, Cohen P, Kwon JS. Clozapine-induced lymphocytic alveolitis. Am J Psychiatry. 2011;168:2–1.
9. Hashimoto N, Maeda T, Okubo R, Narita H, Kusumi I. Simple pulmonary eosinophilia associated with clozapine treatment. J Clin Psychopharmacol. 2015;35:99–101.
10. Aldridge G, Collins C, Croucher M. Clozapine-induced pneumonitis. Aust N Z J Psychiatry. 2013;47:1215–6.
11. Bugge E, Nissen T, Wynn R. Probable clozapine-induced parenchymal lung disease and perimyocarditis: a case report. BMC Psychiatry. 2016;16:438.
12. Lewis A, Gibbs A, Hope-Gill B. Probable occupational pneumonitis caused by inhalation of crushed clozapine. Occup Med. 2012;62:385–7.
13. Nakamura M, Nagamine T. Recurrence of eosinophilic pneumonia after clozapine treatment. Asian J Psychiatr. 2019;44:4–5.
14. Torrico T, Crandall RO, Meza C, Abdijadid S. Clozapine-induced pneumonitis: a case report. Front Psychiatry. 2020;11:572102.
15. Nakamura M, Nagamine T. Eosinophilic pneumonia during treatment with clozapine: reports from a retrospective case series. Int Clin Psychopharmacol. 2020;35(5):285–91.
16. Philit F, Etienne-Mastroïanni B, Parrot A, Guérin C, Robert D, Cordier JF. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med. 2002;166:1235–9.
17. De Giacomi F, Vassallo R, Yi ES, Ryu JH. Acute eosinophilic pneumonia. causes, diagnosis, and management. Am J Respir Crit Care Med. 2018;197(6):728–36.
18. Jang Y, Moon J, Kim N, Kim TJ, Jun JS, Shin YW, et al. A new rapid titration protocol for lamotrigine that reduces the risk of skin rash. Epilepsia Open. 2021;6(2):394–401.
19. de Leon J, Ruan CJ, Verdoux H, Wang C. Clozapine is strongly associated with the risk of pneumonia and inflammation. Gen Psychiatr. 2020;33(2):e100183.
20. de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, et al. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. Pharmacopsychiatry. 2022;55(2):73–86.
21. Maes M, Bosmans E, Kenis G, De Jong R, Smith RS, Meltzer HY. In vivo immunomodulatory effects of clozapine in schizophrenia. Schizophr Res. 1997;26(2–3):221–5.
22. Maes M, Meltzer HY, Bosmans E. Immune-inflammatory markers in schizophrenia: comparison to normal controls and effects of clozapine. Acta Psychiatr Scand. 1994;89(5):346–51.
23. Kohen I, Afzal N, Hussain S, Manu P. Increases in C-reactive protein may predict recurrence of clozapine-induced fever. Ann Pharmacother. 2009;43(1):143–6.
24. Hung YP, Wang CS, Yen CN, Chang HC, Chen PS, Lee IH, et al. Role of cytokine changes in clozapine-induced fever: a cohort prospective study. Psychiatry Clin Neurosci. 2017;71(6):395–402.
25. Pandurangi AK, Buckley PF. Inflammation, antipsychotic drugs, and evidence for effectiveness of anti-inflammatory agents in schizophrenia. Curr Top Behav Neurosci. 2020;44:227–44.
26. Pollmächer T, Hinze-Selch D, Mullington J. Effects of clozapine on plasma cytokine and soluble cytokine receptor levels. J Clin Psychopharmacol. 1996;16(5):403–9.
27. Manu P, Lapitskaya Y, Shaikh A, Nielsen J. Clozapine rechallenge after major adverse effects: clinical guidelines based on 259 cases. Am J Ther. 2018;25(2):e218–23.
28. Bowers P, Rosenkrantz B, Palanci J, Goldsmith D, Cotes R. A slow, cautious, and successful clozapine rechallenge after myocarditis. Prim Care Companion CNS Disord. 2022;24(2):21cr02976.
29. Griffin JM, Woznica E, Gilotra NA, Nucifora FC, Jr. Clozapine-associated myocarditis: a protocol for monitoring upon clozapine initiation and recommendations for how to conduct a clozapine rechallenge. J Clin Psychopharmacol. 2021;41(2):180–5.
30. Shivakumar G, Thomas N, Sollychin M, Takács A, Kolamunna S, Melgar P, et al. Protocol for clozapine rechallenge in a case of clozapine-induced myocarditis. Can J Psychiatry. 2020;65(7):448–53.
31. Yada Y, Kitagawa K, Sakamoto S, Ozawa A, Nakada A, Kashiwagi H, et al. The relationship between plasma clozapine concentration and clinical outcome: a cross-sectional study. Acta Psychiatr Scand. 2021;143(3):227–37.
32. Siskind D, Sharma M, Pawar M, Pearson E, Wagner E, Warren N, et al. Clozapine levels as a predictor for therapeutic response: a systematic review and meta-analysis. Acta Psychiatr Scand. 2021;144(5):422–32.

How to cite this article: Kikuchi Y, Komatsu H, Sakuma A, Tanifuji H, Tomita H. Successful rechallenge with clozapine after discontinuation due to drug-induced pneumonia: a case report. Psychiatry Clin. Neurosci. Rep. 2022;1:e38. https://doi.org/10.1002/pcn5.38