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CASE REPORT

A case of invasive pulmonary aspergillosis associated with clozapine-induced agranulocytosis

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Abstract

Background: Clozapine-induced agranulocytosis (CLIA) is a rare but serious complication. Fever associated with CLIA is typically treated with broad-spectrum antimicrobials, but empiric antifungal therapy is rarely used. While bacterial and viral infections have been reported in CLIA cases, no cases of fungal infections complicated by CLIA have been documented. We report the first case of CLIA complicated by invasive pulmonary aspergillosis (IPA) in a patient with schizophrenia. The diagnosis of IPA was made using serum β-D-glucan, *Aspergillus* galactomannan antigen tests, and chest computed tomography (CT).

Case presentation: We present a case of a 51-year-old man with schizophrenia who developed CLIA complicated by IPA. The patient, diagnosed with treatment-resistant schizophrenia, was started on clozapine, but 9 months later he presented with fever, cough, leukopenia, and neutropenia. Clozapine was discontinued, and empirical treatments with cefepime and filgrastim were initiated. Serum β-D-glucan and *Aspergillus* galactomannan antigen tests were positive, and chest CT showed well-circumscribed nodules, leading to a probable diagnosis of IPA. Antifungal therapy was switched from micafungin to voriconazole according to guidelines. His neutropenia and fever improved, and he was re-transferred to a psychiatric hospital.

Conclusion: CLIA can be complicated by fungal infections. When patients with CLIA present with fever, fungal infections, including IPA, should be considered in the differential diagnosis. Serological tests, including β-D-glucan and *Aspergillus* galactomannan, are useful for the diagnosis of IPA as well as the appropriate use of antifungal agents in patients with CLIA.

KEYWORDS
clozapine-induced agranulocytosis, fungal infections, invasive pulmonary aspergillosis, schizophrenia

BACKGROUND

Clozapine-induced agranulocytosis (CLIA) occurs in 0.4%–0.9% of patients treated with clozapine.[1,2] When CLIA presents with fever, broad-spectrum antimicrobials are administered empirically, but empiric antifungal therapy is not usually provided.[3] Although bacterial or viral infections associated with CLIA have been reported,[4,5] there are no reports of fungal infection complicated by CLIA. Here, we report a case of schizophrenia with CLIA and invasive pulmonary aspergillosis (IPA). We successfully diagnosed IPA using serum β-D-glucan, an *Aspergillus* galactomannan antigen test, and chest computed tomography (CT). To the best of our knowledge, this is the first report of a fungal infection complicated by CLIA.

CASE PRESENTATION

A 51-year-old man with a history of schizophrenia presented with catatonia at a local psychiatric hospital. His medical history was otherwise unremarkable, including no history of diabetes. He had been taking olanzapine for the past 10 years but discontinued medication because his auditory hallucinations relapsed. He was hospitalized and treated with antipsychotics, including olanzapine 20 mg/day and lurasidone 80 mg/day for 3 months, but his psychotic symptoms did not improve, therefore he was diagnosed with treatment-resistant schizophrenia. Clozapine was initiated and the dose was titrated to 250 mg/day. Blood tests were performed every 1–2 weeks to monitor blood cell counts. The patient had poor tolerability to further increases in clozapine dosage due to sedation and constipation. As the improvement in psychiatric symptoms was insufficient, risperidone was added as augmentation therapy 7 months after starting clozapine and was titrated up to 4 mg. Nine months after the initiation of clozapine, he presented with a fever of 38.6°C and a cough. His other vital signs remained stable. His blood count indicated leukopenia and neutropenia (white cell count 1600/μL, absolute neutrophil count 35/μL). He was diagnosed with CLIA and transferred to our university hospital on the same day for treatment in collaboration with the hematology department. On admission, clozapine was discontinued, and he was started on filgrastim 75 μg/day and cefepime 2 g q8h. The sputum culture and the blood culture test were negative. Serum β-D-glucan was detected on day 2 and micafungin 150 mg/day was added as an empirical antifungal treatment. On day 7, *Aspergillus* galactomannan antigen was detected in serum. Non-contrast chest CT revealed dense, well-circumscribed nodules (Figure 1) and he was diagnosed with probable IPA.[6] We changed antifungal agents from micafungin to voriconazole

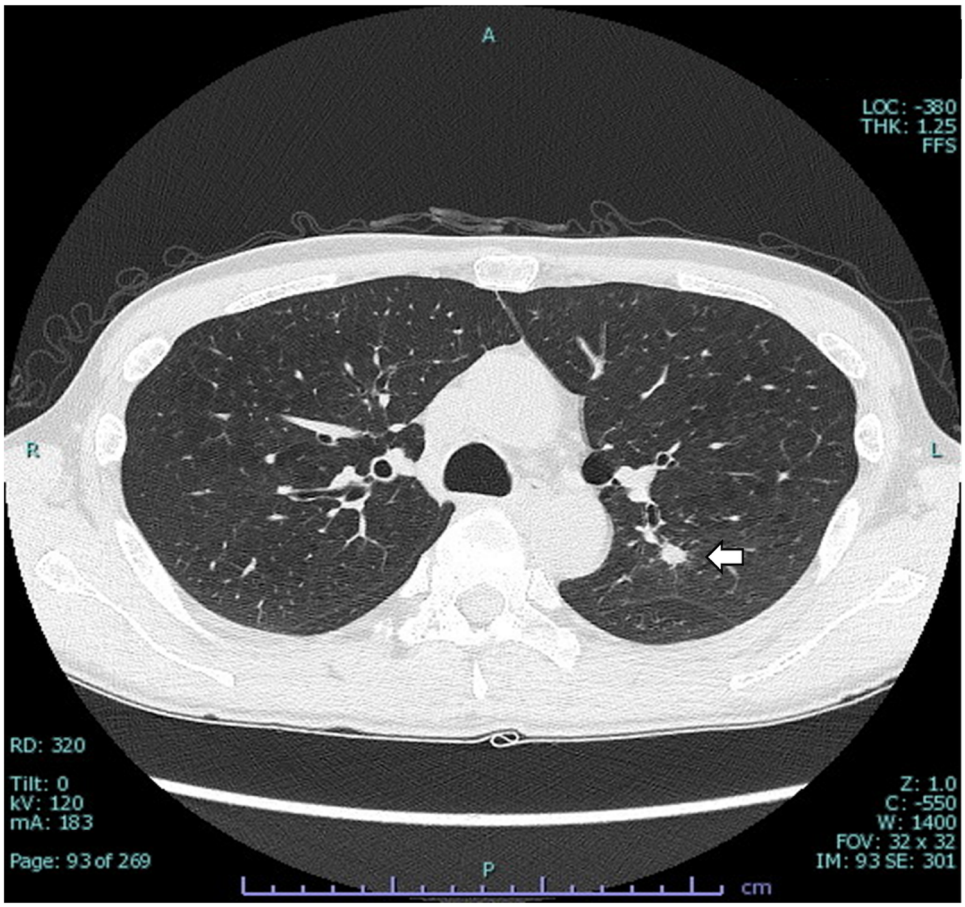

FIGURE 1 Chest computed tomography scan showing a well-circumscribed nodular lesion in the left upper lobe (arrow).

400 mg/day according to the current guidelines for aspergillosis.[3] Because his fever and neutropenia improved, filgrastim and cefepime were discontinued on day 9. On day 13, he was re-transferred to the local psychiatric hospital for continued psychiatric treatment. Risperidone 4 mg/day was continued and delusion persisted. The duration of voriconazole treatment was until the nodules disappeared on CT chest images (Figure 2). The course of treatment is shown in Figure 3.

DISCUSSION

This is the first case report of a fungal infection and IPA complicated by CLIA. In this case, IPA was diagnosed at an early stage of fever by combined tests for β-D-glucan and *Aspergillus* antigen. In general, empiric antifungal therapy is not recommended for febrile neutropenia without prolonged neutropenia or persistent fever, and neutropenia for more than 10 days is a risk for fungal infection.[3] Because the median number of days to recovery from CLIA was reported to be 10 days (range 2–68 days),[7] an examination for fungal infection is required. Furthermore, the early initiation of antifungal treatment is warranted for patients with strongly suspected IPA.[3] Because invasive fungal infections are a major cause of morbidity and mortality in immunocompromised patients, prompt diagnosis using serological tests and initiation of preemptive antifungal treatment may help avoid serious complications in CLIA patients.

In this case, the use of combined tests for β-D-glucan and *Aspergillus* antigen enabled the differentiation of invasive aspergillosis from other fungal infections, leading to the appropriate antifungal drug administration. In neutropenic patients, micafungin is tolerated better than voriconazole,[8] and it is widely used as an empiric antifungal therapy, especially in patients with suspected *Candida* infection. However, voriconazole, but not micafungin, is recommended as an initial treatment for IPA because limited data are available for echinocandins, including micafungin, as primary therapy.[3] Therefore, it is important to differentiate *Aspergillus* infection from other fungal infections, especially when respiratory symptoms are present and CT chest imaging reveals well-circumscribed nodules in CLIA patients.

A proven diagnosis of IPA requires histopathological evidence of mycelium with tissue damage or the detection of *Aspergillus* spp. by the culture of specimens obtained from lung biopsies.[6] These tests have low sensitivity, and immunocompromised patients have a higher risk for complications of transbronchial lung biopsy or bronchoalveolar lavage.[9] Noninvasive serological tests may be useful for

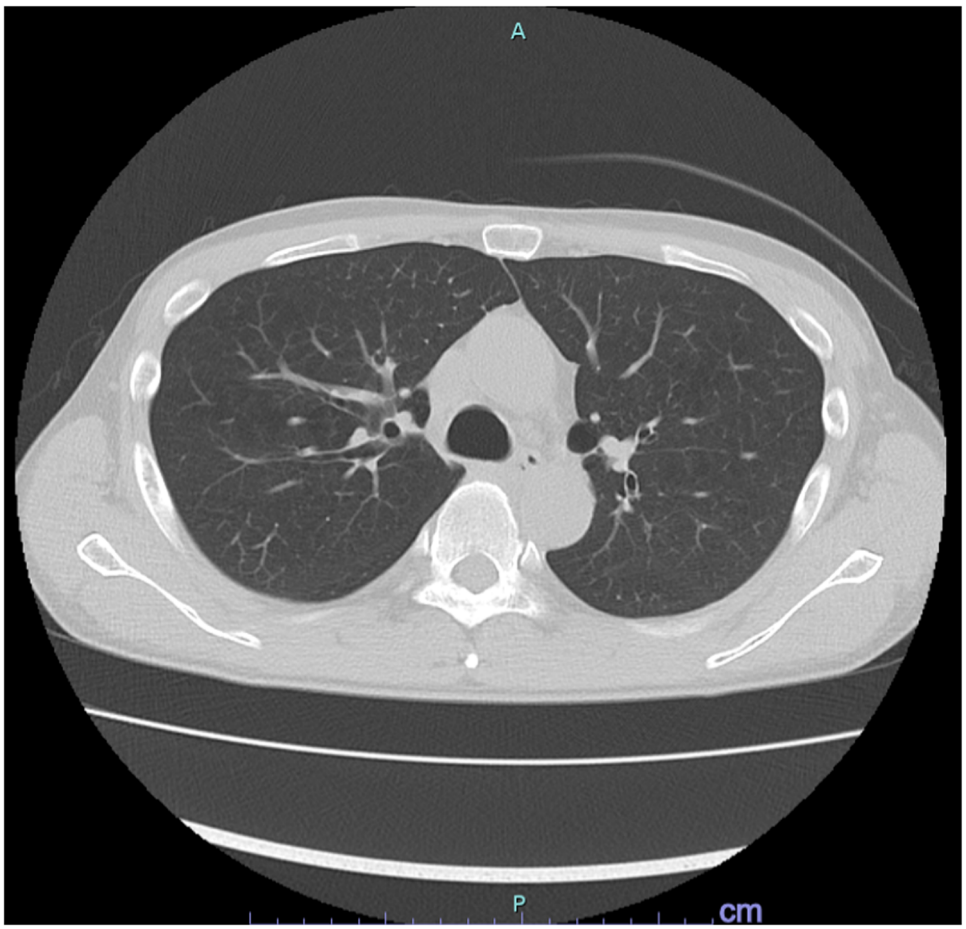

FIGURE 2 One month after the transfer, a chest computed tomography scan showed that the nodular lesion had disappeared.

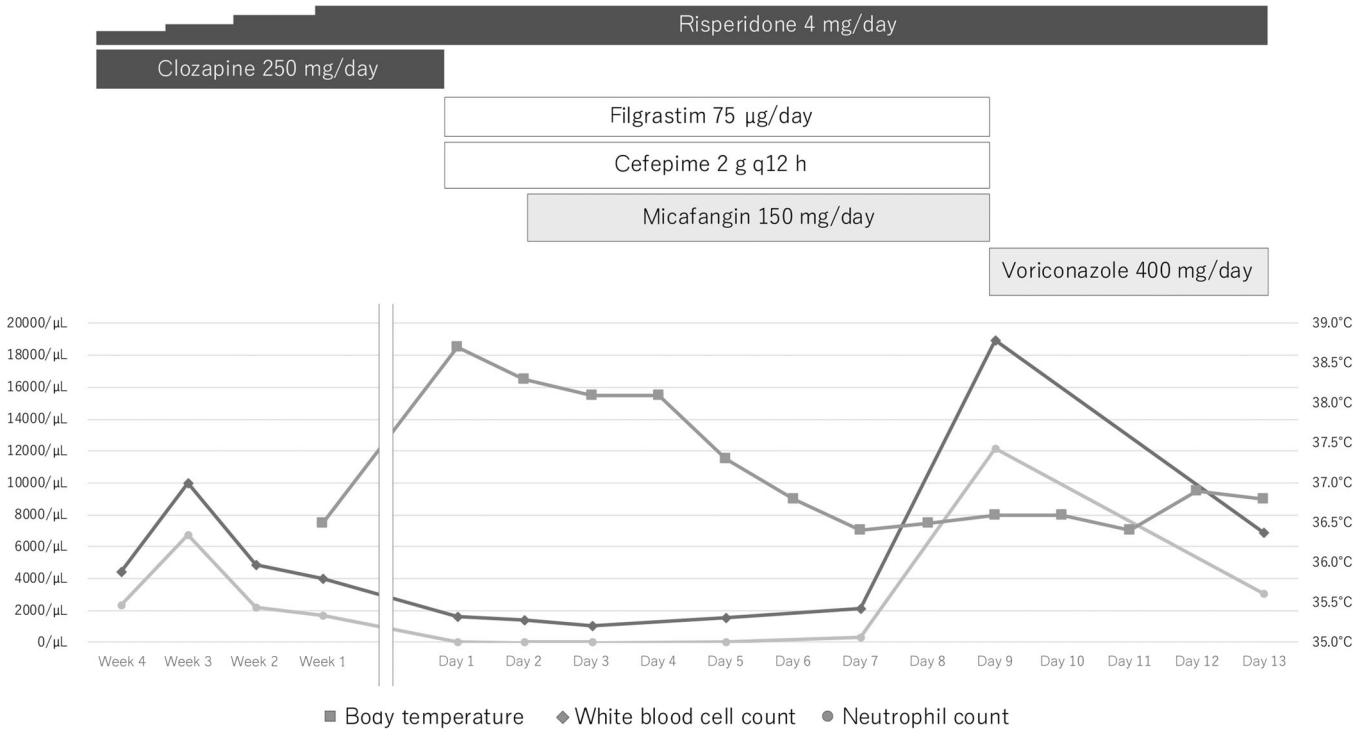

FIGURE 3 Progress chart showing temperature and blood counts. On the left of the two lines are the results of weekly blood tests prior to admission. wk, week.

immunocompromised CLIA patients with psychotic symptoms because invasive diagnostic tests may be difficult to perform in these patients.

CLIA is most commonly observed within the first 6 months after the initiation of clozapine. However, a study investigating the onset timing of CLIA reported that 21% of cases occurred after 6 months.[10] In cases of late-onset agranulocytosis, it is essential to rule out the possibility of neutropenia caused by medications other than clozapine. In this case, the improvement in the neutrophil count after discontinuing clozapine suggests that risperidone-induced neutropenia is unlikely, and clozapine is considered the causative drug.

When selecting an alternative antipsychotic to clozapine under antifungal therapy, caution must be exercised due to potential drug interactions. Voriconazole is metabolized by cytochrome P450 enzymes, including CYP2C9, CYP2C19, and CYP3A4, and it inhibits CYP3A4. As a result, several antipsychotic drugs are contraindicated for co-administration according to Japanese package inserts. Risperidone is partially metabolized by CYP3A4, so caution is required when using these medications together.[11] Adverse effects, including QT prolongation, were monitored and no adverse events were observed.

CONCLUSION

In conclusion, CLIA can be complicated by fungal infections. When patients with CLIA present with fever, fungal infections including IPA should be considered in the differential diagnosis. The above serological tests are useful for the diagnosis of IPA as well as the appropriate use of antifungal agents in CLIA patients.

AUTHOR CONTRIBUTIONS

Akiyoshi Yokode: Conceptualization; literature search; writing—original draft. **Masaki Fujiwara:** Conceptualization; project administration; supervision; writing—review and editing. **Toshiki Terao:** Conceptualization; writing—review and editing. **Shinji Sakamoto:** Conceptualization; writing—review and editing. **Yuto Yamada:** Conceptualization; writing—review and editing. **Ryota Sato:** Conceptualization; writing—review and editing. **Momoko Mishima:** Conceptualization; writing—review and editing. **Yuji Yada:** Conceptualization; writing—review and editing. **Ken-Ichi Matsuoka:** Conceptualization; writing—review and editing. **Manabu Takaki:** Conceptualization; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

Akiyoshi Yokode declares no conflict of interest. Masaki Fujiwara reports personal fees from Mochida and Eizai outside the submitted work. Manabu Takaki reports personal fees from Otsuka, Viatris, Takeda, Sumitomo Pharma, Meiji, and Eizai outside the submitted work. Manabu Takaki is an Editorial Board member of *Psychiatry and Clinical Neurosciences Reports* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making

related to the acceptance of this article for publication. Shinji Sakamoto personal fees from Otsuka, Meiji, Kyowa, and Eizai outside the submitted work. Yuto Yamada reports personal fees from Meiji and Sumitomo Pharma outside the submitted work. Yuji Yada reports personal fees from Otsuka and Sumitomo Pharma outside the submitted work. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

N/A.

ETHICS APPROVAL STATEMENT

This is a case report which does not require ethics committee approval.

PATIENT CONSENT STATEMENT

Written informed consent for publication was obtained from the surrogate of the patient.

CLINICAL TRIAL REGISTRATION

N/A.

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