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*Case Report*

# COVID-19 associated pulmonary aspergillosis

COVID-19 Associated Pulmonary Aspergillosis

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**Abstract**
During the COVID-19 pandemic, invasive fungal infections, particularly pulmonary aspergillosis, became a significant health issue in immunocompromised patients. This case report discusses a patient diagnosed with hairy cell leukemia who developed neutropenia following cladribine chemotherapy and subsequently experienced a complicated case of invasive pulmonary aspergillosis associated with COVID-19. The treatment process and outcomes provide important insights into the management of COVID-19-associated invasive pulmonary aspergillosis (CAPA). The patient was diagnosed with invasive aspergillosis during COVID-19 treatment and achieved a successful recovery with voriconazole therapy.

**Keywords**
COVID-19, Pulmonary Aspergillosis, Voriconazole, Neutropenia, Hairy Cell Leukemia, CAPA

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## Introduction

Pulmonary aspergillosis is known as a serious opportunistic infection in immunocompromised patients, and a significant increase in the incidence of this infection has been observed during the COVID-19 pandemic. The incidence of invasive pulmonary aspergillosis in COVID-19 patients has been reported to vary between 19.6% and 33.3%, and the mortality rate of this disease can be as high as 64.7% [1, 2]. In this case report, we present a patient with a diagnosis of Hairy cell leukemia who developed invasive pulmonary aspergillosis during COVID-19 infection, as we believe that sharing clinical experience may be important. Informed consent was obtained from the patient.

## Case Report

A 41-year-old male patient diagnosed with hairy cell leukemia was admitted to our hospital with the diagnosis of neutropenic fever that occurred after cladribine chemotherapy. The patient was empirically started on piperacillin-tazobactam. However, when the patient's infective markers showed progression, and the fever continued, the treatment was changed to meropenem+teicoplanin. No growth was observed in the cultures. Clinical and laboratory responses were observed in the patient from the third day of the new treatment combination.

G-CSF treatment was given upon the development of pancytopenia. Endoscopy was planned for the patient, who also complained of difficulty swallowing, with suspicion of candida esophagitis, and the COVID-19 PCR test taken before the procedure resulted positive. Fluconazole treatment was started for esophagitis. No COVID-19 pneumonic infiltration was detected in the thorax CT. On the 8th day of COVID-19 treatment, the patient experienced respiratory distress and an increase in infection markers (procalcitonin, CRP), and 250 mg methylprednisolone (3 days) was added to his treatment.

On the 9th day of COVID-19 treatment, thoracic CT revealed consolidation areas consistent with invasive aspergillosis. A sputum culture and galactomannan antigen test sample were taken from the patient. After a positive aspergillosis finding on CT, a sputum culture was sent in the morning on an empty stomach for three consecutive days. The samples taken were first examined under a direct microscope with calcofluor white-KOH. Then, they were planted on abuse dextrose agar. There was no growth in all three cultures during the 1-month incubation period. Galactomannan antigen was found positive. The patient was started on voriconazole treatment, and a decrease in respiratory distress and oxygen requirement was observed. In addition, the patient's neutropenic condition improved. Upon regression of infectious markers, the patient's meropenem+teicoplanin treatment was discontinued on the 24th day.

The patient was discharged with oral voriconazole treatment. Voriconazole was initially started at 400 mg PO twice daily and then continued at 200 mg po twice daily. In the control thorax CT performed during the 1st month of voriconazole treatment, significant regression of infiltrations was observed. It was decided to continue the treatment until the infiltration areas completely disappeared. In the 12th week of treatment, the infiltration areas completely disappeared, and the treatment was terminated.

## Discussion

During the COVID-19 pandemic, there has been a significant increase in the incidence of invasive fungal infections (IFE), especially in immunocompromised patients receiving treatment in intensive care units. One of the most striking of these infections is invasive pulmonary aspergillosis (IPA). Fungal events accompanying respiratory tract infections are a serious cause of complications, especially in immunocompromised COVID-19 patients. This condition has been included in the literature as COVID-19-associated pulmonary aspergillosis (CAPA). The effect of SARS CoV-2 on the immune system and immunosuppressive treatments increase the risk of developing such invasive infections [1, 3]. In our case, neutropenia developing after cladribine chemotherapy and COVID-19 together paved the way for pulmonary aspergillosis.

In addition, complications such as acute respiratory distress syndrome (ARDS) caused by COVID-19 infection increase the risk of developing pulmonary aspergillosis. Therefore, the presence of invasive fungal infections in respiratory tract infections complicated by COVID-19 should not be ignored. In high-risk patient groups, additional tests should be performed with a more aggressive approach for the diagnosis of CAPA, and prophylaxis or treatment should be started early. Especially in cases where the galactomannan test and CT findings are positive, antifungal treatment should be started immediately [4, 5]. In our case, when the galactomannan antigen test was taken immediately after the aspergillosis-compatible CT finding was observed and it was determined positive, voriconazole treatment was started without delay. In this case, the development of CAPA in a patient receiving chemotherapy with the diagnosis of Hairy cell leukemia was investigated. Neutropenia in these patients constitutes an important risk factor for fungal infections. Clinical recognition of pulmonary aspergillosis developing during COVID-19 infection may be difficult because it may present with similar respiratory symptoms to COVID-19. Therefore, high clinical suspicion and early diagnostic methods are critical for the success of treatment. Histopathological examination, sputum culture, bronchoalveolar lavage (BAL) culture, aspergillus PCR, serum galactomannan, BAL galactomannan, direct radiography, and computed tomography are used in the diagnosis of CAPA [6]. In our case, histopathological examination could not be performed, and aspergillus spp did not grow in the sputum culture, but the diagnosis was made with high clinical suspicion, imaging compatible with aspergillosis and galactomannan antigen positivity.

Voriconazole and isavuconazole are the first-line antifungal agents used in CAPA treatment. However, in cases of voriconazole resistance, side effects, and drug interactions, liposomal amphotericin B is the first drug to be used as an alternative to these drugs. Alternative second-line options are posaconazole or echinocandins. Echinocandins should not be used as monotherapy if other options remain, but they can be used as salvage therapy. In this case, a successful result was obtained with early antifungal treatment. Voriconazole treatment plays an important role in reducing mortality in CAPA cases. Voriconazole should be given as a loading dose of 6 mg/kg twice daily on the first day, followed by a maintenance dose

of 4 mg/kg twice daily, and liposomal amphotericin B should be administered at a dose of 3 mg/kg daily. Although the treatment period is stated as 6-12 weeks, the treatment period may be longer in immunocompromised patients, depending on the patient's clinic, radiological findings, and galactomannan antigen monitoring [7].

*Conclusion*

Pulmonary aspergillosis is more common in patients with COVID-19 infection, especially in the presence of complications such as immunosuppressive conditions or ARDS, and has high mortality rates. Voriconazole is the first-line agent in the treatment of CAPA. Caution should be exercised in terms of pulmonary aspergillosis in COVID-19 patients, and early antifungal therapy should be initiated if necessary.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.*

***Conflict of interest***

*The authors declare that there is no conflict of interest.*

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