

[ CASE REPORT ]

## Successful Treatment of Antifungal Combination Therapy with Inhaled Liposomal Amphotericin B and Oral Voriconazole for Intractable Chronic Progressive Pulmonary Aspergillosis

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### Abstract:

We experienced a case of the successful treatment of intractable pulmonary aspergillosis with inhaled liposomal amphotericin B (L-AMB) and oral voriconazole (VRCZ). A 52-year-old man was admitted to our hospital with a fever. Chest computed tomography (CT) revealed an infiltrative shadow. Two separate sputum cultures detected *Aspergillus niger*. Although we treated the patient with single and combined antifungal agents, the infiltrative shadow worsened. After obtaining sufficient informed consent from the patient, we switched him to an inhaled L-AMB. The infiltrative shadow subsequently improved. The patient has remained well for one year without exacerbation. We herein report the usefulness of inhaled L-AMB and oral VRCZ.

**Key words:** chronic progressive pulmonary aspergillosis, fungus ball, inhaled liposomal amphotericin B, antifungal combination therapy, *Aspergillus niger*

(Intern Med 60: 2465-2468, 2021)

(DOI: 10.2169/internalmedicine.6305-20)

### Introduction

The Japanese domestic guidelines (1) for chronic progressive pulmonary aspergillosis (CPPA), which is referred to as chronic cavitary pulmonary aspergillosis in the European guidelines (2), recommend monotherapy, such as micafungin (MCFG) or voriconazole (VRCZ), as the first-line treatment. However, no treatment for CPPA that is intractable to antifungal therapy has yet been reported.

In cases of intractable invasive pulmonary aspergillosis (IPA), antifungal combination therapy is recommended in the guidelines (1, 3), and surgical resection is the first choice in the guidelines for simple pulmonary aspergilloma with a fungus ball (FB) (1, 4). However, both of these therapies proved ineffective and inadequate in the present patient.

There are several reviews and reports on the usefulness of inhalation treatment with L-AMB for IPA, allergic pulmonary aspergillosis and *Aspergillus empyema* (5-9). However, the efficacy of L-AMB inhalation therapy for intractable CPPA caused by *Aspergillus niger* has not been reported.

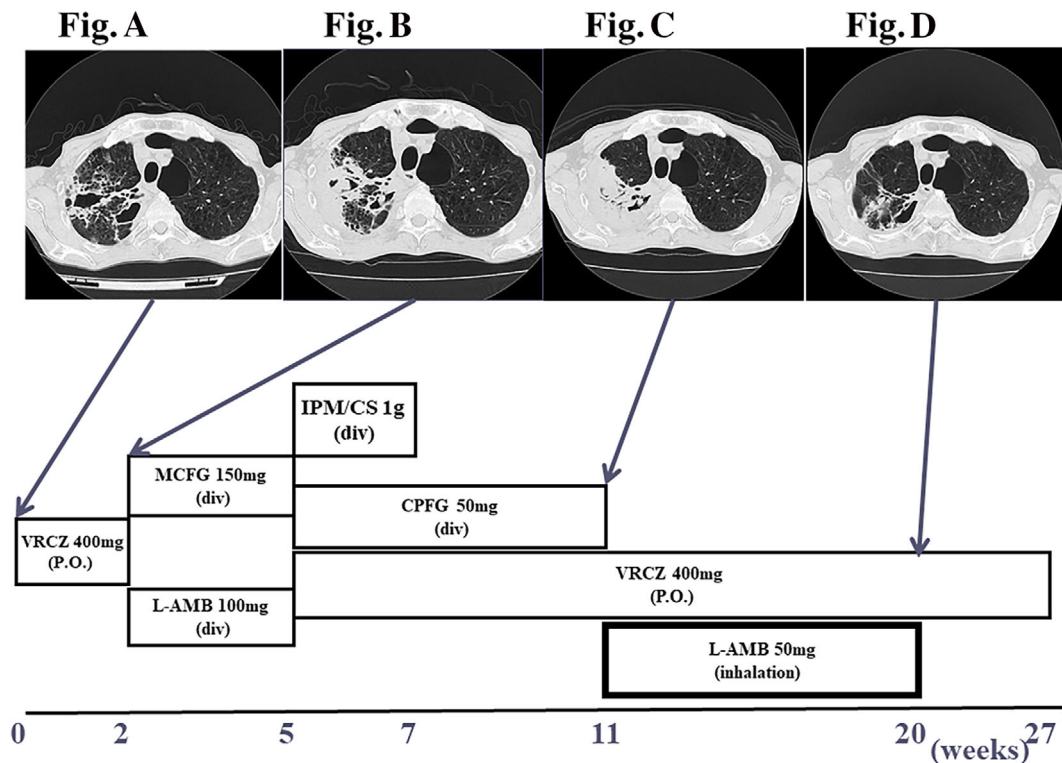
We herein report a valuable case of L-AMB inhalation and oral VRCZ treatment for intractable CPPA caused by *A. niger*.

### Case Report

A 52-year-old man admitted to our hospital with the complaints of a fever and hemoptysis. He had underlying pulmonary emphysema and had been treated for nontuberculous mycobacteriosis for about two years previously.

He was 170 cm tall and weighed 42 kg. Other physical

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Received: September 13, 2020; Accepted: January 12, 2021; Advance Publication by J-STAGE: March 8, 2021  
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**Figure.** The patient's clinical course. A chest computed tomographic scan showing the patient's condition at admission (Figure A), the appearance of a new fungus ball (Figure B) and worsening infiltrate around the cavity (Figure C) with each intravenous administration of various antifungal agents. This condition improved after the completion of L-AMB administration (Figure D).

examinations revealed no significant findings. Laboratory tests showed that the white blood cell count, C-reactive protein, and beta-D-glucan levels and *Aspergillus* galactomannan antigen were increased (10,400/ $\mu$ L, 16.47 mg/dL, 26.6 pg/mL, and 1.3 respectively). However, no measurement was made for immunoglobulin G against *Aspergillus*. Initial computed tomography (CT) revealed an infiltrative shadow around a preexisting cavity in the right upper lobe accompanied by a low-attenuation area showing pulmonary emphysema. (Fig. A). Two separate sputum cultures were positive for *Aspergillus niger*, but calcium oxalate crystals could not be confirmed under a polarizing microscope of sputum culture samples. At this point, the species of *A. niger* was not identified using a molecular genetic approach (10).

Bronchoscopy was planned for a definitive diagnosis but could not be performed because the patient refused. Nontuberculous mycobacteria was not detected on mycobacterial staining. We considered this case to be a complication of *Aspergillus* infection rather than exacerbation of nontuberculous mycobacterial infection. Allergic bronchopulmonary aspergillosis was not positively considered, as there were no asthmatic symptoms, such as paroxysmal dyspnea or peripheral blood eosinophilia.

The patient was first treated with oral VRCZ 400 mg/day for 2 weeks. Follow-up CT revealed an enlarged infiltrative shadows and the formation of new FBs within the cavity (Fig. B). Monitoring the drug for VRCZ was necessary to determine the effectiveness of VRCZ, but we were unable to

do it because we focused on choosing the next drug. We sequentially treated the patient with intravenous combined antifungal drugs including MCFG 150 mg/day and L-AMB 2.5 mg/kg or 100 mg/day for 3 weeks, followed by combined with CPFG 50 mg/day and VRCZ 400 mg/day for 6 weeks. Despite these various antifungal combination therapies, the infiltrative shadow worsened (Fig. C). Drug susceptibility testing for *A. niger* should have been performed, but unfortunately, we did not conduct it. We therefore considered surgical resection of the lesion, but this option was rejected by the surgeon because of the risk of bleeding and new infection.

We then carefully searched the literature and learned about inhalation therapy with L-AMB for intractable pulmonary aspergillosis. Finally, we obtained full informed consent from our patient and his family to administer inhaled L-AMB. Antifungal combination therapy was therefore started with an inhaled L-AMB twice daily at a dose of 25 mg along with oral VRCZ 400 mg per day according to the previously reported method (5). Purcell et al. reported that patients safely inhaled 50 mg of L-AMB twice a day, but since our patient weighed only 42 kg, which was substantially lighter than the previously evaluated patients, he inhaled 25 mg twice a day. Specifically, L-AMB 50 mg was dissolved in 12 mL of normal saline solution, of which 6 mL (contains 25 mg of L-AMB) was inhaled 2 times in the morning and evening. An ultrasonic nebulizer U 17 made by OMRON (Kyoto, Japan) was used for the inhaler.

The patient's clinical symptoms, such as his fever and cough, began to improve after two weeks of treatment without side effects of bronchospasm, such as coughing. We continued the antifungal combination therapy for seven weeks, and follow-up CT revealed the further improvement of the infiltrative shadows and reduction in size of the FB (Fig. D). The patient then continued oral VRCZ as an outpatient for four more months. Since finishing his treatment for CPPA, he has been well for one year without exacerbation.

## Discussion

We herein report a case of intractable CPPA caused by *A. niger* successfully treated with antifungal combination therapy of inhaled L-AMB and VRCZ. To our knowledge, this therapy has never been reported and is a completely new therapy for intractable CPPA (1, 4). MCFG or VRCZ is recommended (in that order) as the first choice for CPPA treatment guidelines (1, 3). This is because no significant difference in the efficacy rate was noted in a comparative study of MCFG and VRCZ against a CPPA, although the side effect rates were 26.4% for MCFG and 61.1% for VRCZ, showing an extremely low rate for MCFG. However, there have been no comparative studies for cases of intractable CPPA, and there is currently no recommended treatment for intractable CPPA in the guidelines.

In cases of intractable IPA, antifungal combination therapy is listed as a treatment option (11). Therefore, we treated the present patient with a combination of antifungal agents, but his condition did not improve. There have been several reviews and reports on the usefulness of inhalation therapy with L-AMB for the prevention of IPA in immunocompromised hosts (6), for allergic bronchopulmonary aspergillosis (7), and for *Aspergillus* empyema (5, 9). When we performed antifungal combination therapy with inhaled L-AMB and oral VRCZ after obtaining sufficient Informed consent from the patient and his family, his condition improved. We then checked the literature for clues concerning the treatment of FB. Surgical resection is the first choice for simple pulmonary aspergilloma in the guidelines (1, 4). According to the report by Lee et al., the 10-year survival rate with simple pulmonary aspergilloma was 84.6% in the operation group and 56.7% in the non-operation group, showing a good prognosis in the operation group (12). However, in the present patient, the surgeon declined to perform surgical resection because of the risk of bleeding and new infection.

Effective alternatives to surgical resection include cavernoscopic removal of a FB (13) or CT-guided intracavitary injection of amphotericin B (14). However, these treatments are complex and carry a risk of death. We were thus left with no choice but to obtain sufficient informed consent from the patient and his family to attempt L-AMB inhalation therapy in addition to oral VRCZ. As a result, the size of the FB was significantly reduced, and his condition improved without any problems.

On reviewing the clinical course of our case, no therapeutic effect was observed with the intravenous injection of L-AMB or the oral administration of VRCZ; efficacy only appeared after switching the administration method to inhaled L-AMB. We checked the literature for possible reasons for this result. According to Gavalda et al. (15), inhaled antifungal therapy may increase the drug concentration at the site of infection compared to intravenous administration. In addition, Araujo et al. reported that a high deep body temperature reduced the growth ability of *A. niger* compared with *A. fumigatus* (16). Therefore, our case in which *A. niger* had proliferated suggests that the deep body temperature was relatively low, indicating that the ventilation efficiency was good. These results suggest that inhalation of L-AMB may have been effective for reducing the infectious lesion.

While it has been reported that inhaled amphotericin B deoxycholate causes some side effects, such as coughing and dyspnea (17), inhaled L-AMB therapy reportedly has less frequent side effects than amphotericin B deoxycholic acid. Indeed, few side effects seen in our case. However, the therapeutic effect of inhaled L-AMB therapy alone in combination with oral VRCZ has not been completely proven. Further studies are thus needed to clarify the validity of this treatment approach.

## Conclusion

We encountered a case of the successful treatment of intractable CPPA with antifungal combination therapy of inhaled L-AMB and oral VRCZ. Doctors managing *Aspergillus* infections should consider the usefulness of an inhaled approach to L-AMB therapy, which increases the local drug tissue concentration with relatively few side effects, for intractable CPPA.

**The authors state that they have no Conflict of Interest (COI).**

## Acknowledgement

We are grateful to the patient and his family for their cooperation with this research.

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