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Case Report

Successful treatment of *Aspergillus* empyema using combined intrathoracic and intravenous administration of voriconazole: A case report☆

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ABSTRACT

Aspergillus empyema is treated with either systemic administration of antifungal drugs or surgery, but the mortality rate is very high. Here, we report a case of *Aspergillus* empyema successfully treated using combined intrathoracic and intravenous administration of voriconazole (VRCZ). Treatment success was achieved by monitoring VRCZ plasma trough concentration. The patient was a 71-year-old Japanese woman diagnosed with *Aspergillus* empyema whom we started on intravenous administration of VRCZ. Although penetration of VRCZ into the pleural effusion was confirmed, the level was below 1 μg/mL, which is the minimum inhibitory concentration for *Aspergillus fumigatus* determined by antifungal susceptibility testing in pleural effusion culture. Therefore, we initiated combination therapy with intrathoracic and intravenous administration of VRCZ. VRCZ 200 mg was first dissolved in 50–100 mL of saline and administered into the thoracic cavity via a chest tube. The chest tube was clamped for 5–6 h, and then VRCZ solution was excreted though the chest tube. When a single dose of the VRCZ was administered into the intrathoracic space, the plasma concentration before intravenous administration increased from 1.45 μg/mL on day 27 to 1.53 μg/mL on day 28. Although intravenous administration was continued, the VRCZ plasma trough concentration decreased to 1.36 μg/mL on day 29. We therefore decided on an intrathoracic administration schedule of 2–3 times a week. Intrathoracic administration was performed 14 times in total until fenestration surgery on day 64. Our case suggests that combined intrathoracic and intravenous administration of VRCZ may be a valid treatment option for *Aspergillus* empyema.

1. Introduction

Pulmonary aspergillosis is the most serious fungal infections, such as aspergilloma, invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, and allergic bronchopulmonary aspergillosis, but *Aspergillus* empyema is rare [1]. Systemic antifungal agents and surgery are generally selected as treatments [2,3], but the mortality rate of *Aspergillus* empyema remains very high [4]. If the patient's condition cannot be improved through the administration of intravenous antifungal agents, there are few alternative treatment strategies based on available evidence. Voriconazole (VRCZ) is the first-choice drug for the treatment of invasive pulmonary aspergillosis [5]. Because VRCZ has a narrow therapeutic range and is associated with adverse effects such as hepatic injury and vision abnormalities, therapeutic drug monitoring is recommended [6]. Although some reports have examined the penetration ratio of intravenously administered VRCZ to the pleural effusion during empyema treatment [7–9], there are no reports on the effects of intrathoracic administration of VRCZ on drug plasma levels. Here, we report the successful treatment of *Aspergillus* empyema by combined intrathoracic and intravenous VRCZ administration with

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monitoring of its plasma and pleural fluid concentrations. Ethical approval was obtained from the medical research ethics committee at Chiba University (No. 3576).

2. Case report

The patient was a 71-year-old Japanese woman. Her medical history included pulmonary emphysema and interstitial pneumonia. She was suspected of having antineutrophil cytoplasmic antibody-associated vasculitis and was undergoing immunotherapy with prednisolone and azathioprine at another hospital. Four days before admission to our hospital, she developed right pneumothorax with cough, back pain, and dyspnea. Although a chest tube was inserted (right sixth intercostal space, 22 Fr, and 25-cm fixation), her condition did not improve. She was therefore transferred to our hospital. On admission, her temperature at admission was 37 °C, and serum CRP level was 11.0 mg/dL. She was taking codeine phosphate tablets and had no chest pain or dyspnea. Chest computed tomography (CT) images at admission revealed pulmonary emphysema and subcutaneous emphysema. Many septal cavities were widely distributed on both sides of the lung field, and honeycomb lung was evident in the bilateral lower lobe. In the anterior segment of the right upper lobe (S3), there was a cavity shadow with a fungal ball-like structure suggestive of aspergilloma and an infiltrative shadow around the infected cavity (Fig. 1A).

To close the fistula, we administered body tissue adhesive. On day 8 after admission, positive results were obtained for *Aspergillus* antibody. On day 14, the drained pleural effusion appeared cloudy and contained substances like fungus ball. The patient was clinically diagnosed as having *Aspergillus* empyema with rupture of aspergilloma cavity (Fig. 1B). We identified the species as *Aspergillus fumigatus* from pleural effusion collected on day14 and confirmed the diagnosis as *Aspergillus* empyema on day 23. The huge fistula was formed and air leaks persisted, therefore, fenestration was scheduled. Until fenestration, control of infection with antifungal treatment was started. Therefore, intravenous administration of VRCZ was started on day 14 after admission. Serum creatinine was 0.38 on day 14, so we judged her renal function was normal. In addition, the steroid dose was gradually tapered.

Figure 2 shows the changes in VRCZ dosages over time, along with its plasma and pleural effusion concentrations and clinical laboratory values. On day 14, we intravenously administered VRCZ 150 mg. On day 15, we administered VRCZ 150 mg and 100 mg after 12 h followed by 100 mg every 12 h. From day 16, VRCZ 100 mg was administered twice daily. The VRCZ plasma trough concentrations on days 18 and 21 were 1.84 and 1.10 μg/mL, respectively. The VRCZ concentrations in the pleural effusion collected on days 19 and 26 were 0.20 and 0.58 μg/mL, respectively. Antifungal susceptibility testing of *Aspergillus fumigatus* grown from pleural effusion cultures obtained before VRCZ administration on day14 indicated a minimum inhibitory concentration of 1 μg/mL using CLSI M38 A2-compliant microdilutions. On day 25, her body temperature and serum CRP level was 37.4 °C and 2.5 mg/dL, respectively. Chest CT scan on day 27 showed improvement in pneumothorax, but no improvement in empyema status (Fig. 1C). Therefore we judged that the pleural effusion concentration of VRCZ was insufficient. So we began intrathoracic administration of VRCZ from day 27 in combination with intravenous administration.

On day 27, the plasma concentration of VRCZ was 1.45 μg/mL. On the same day, we dissolved 200 mg VRCZ in 50–100 mL of saline for intrathoracic administration. The VRCZ solution was injected through the chest tube and the tube was clamped for 5–6 h. After that, VRCZ solution was excreted through the chest tube. VRCZ plasma concentrations before the intravenous administration were 1.53 μg/mL and 1.36 μg/mL on days 28 and 29, respectively. From these results, we decided on an intrathoracic administration schedule of 2–3 times a week. On day 35, pleural effusion concentration of VRCZ excreted through chest tube was 135.97 μg/mL. Plasma trough concentration of VRCZ did not remarkably change after started intrathoracic administration.

We gradually increased the intravenous dose of VRCZ to improve its efficacy and carefully monitored the plasma concentration of VRCZ and laboratory data on hepatic and renal function. From day 32, we increased the VRCZ dosage to 150 mg twice daily, and the plasma concentration increased from 2.14 μg/mL on day 26

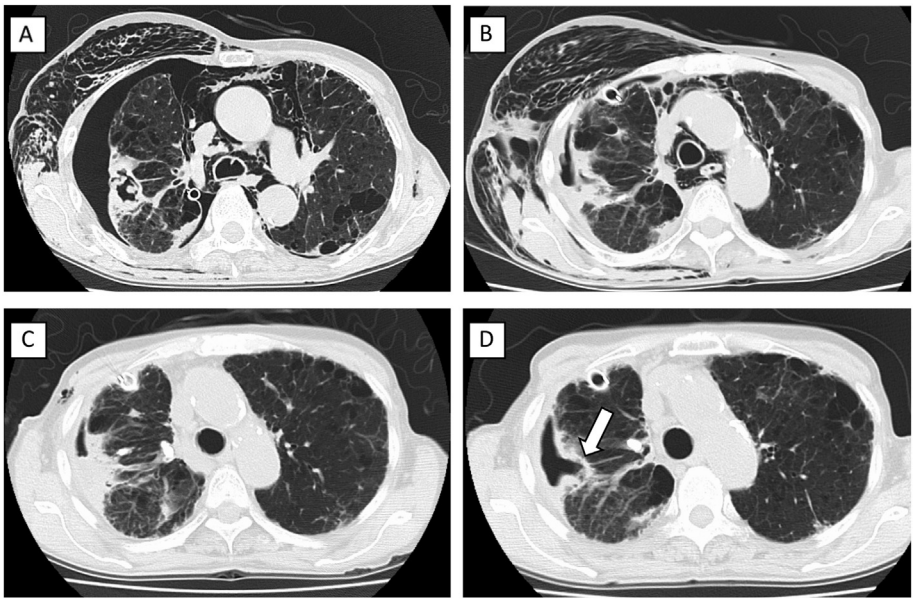

Fig. 1. Chest Computed tomography (CT) images. (A) Day 1. Pulmonary emphysema and subcutaneous emphysema. (B) Day 14. *Aspergillus* empyema with rupture of aspergilloma cavity. (C) Day 27. Improvement in pneumothorax, but no improvement in empyema status with intravenous VRCZ administration. (D) Day 39. The disappearance of the fungus ball (open arrow) after four intrathoracic injections.

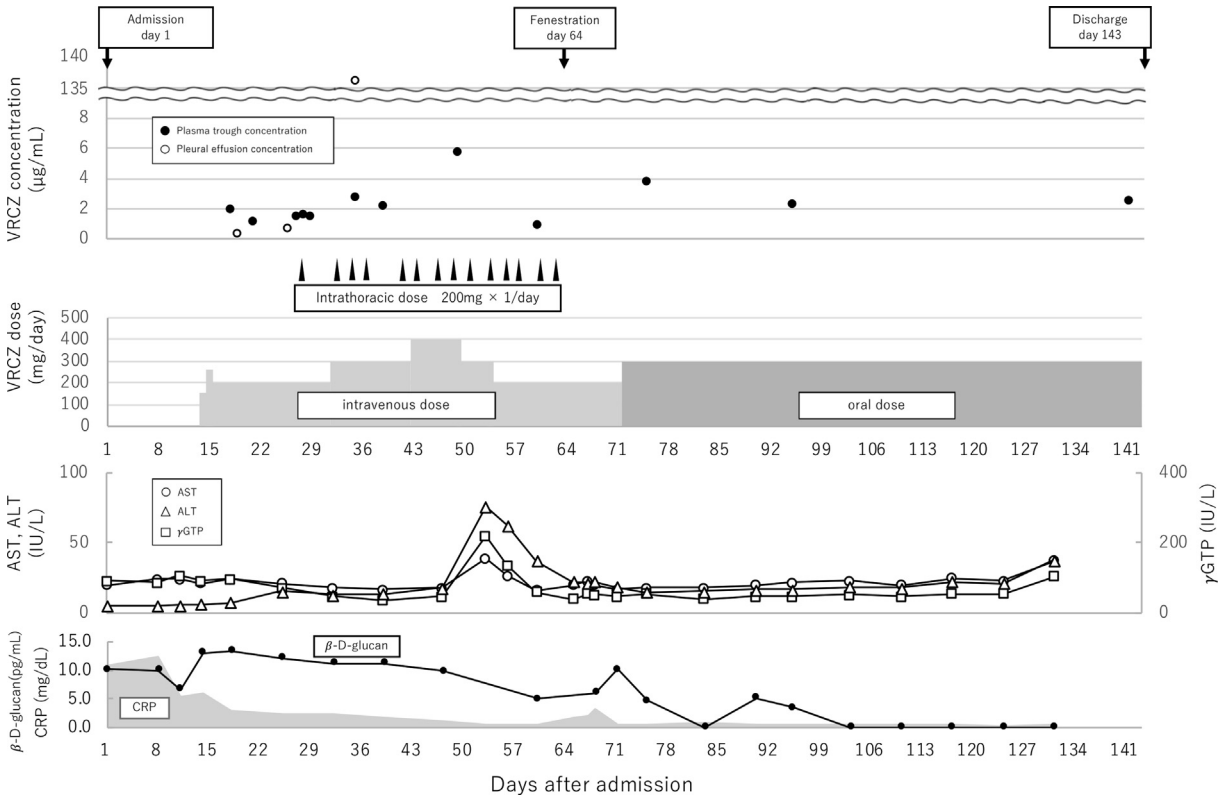

Fig. 2. Timeline of clinical course. VRCZ dosages, VRCZ plasma trough and pleural effusion concentrations and clinical laboratory values. VRCZ: Voriconazole, AST: aspartate transaminase, ALT: alanine aminotransferase, γGTP: gamma glutamyl transpeptidase, CRP: C-reactive protein. Intrathoracic dose was shown as arrows. The measurement time of pleural effusion concentration of days 19, 26, and 35 were 1 p.m., 3 p.m., 9:30 a.m., respectively.

to 2.73 μg/mL on day 35. Based on these results, we increased the VRCZ dosage to 200 mg twice daily to increase the treatment intensity from day 43. However, the plasma concentration had nonlinearly increased to 5.63 μg/mL at day 49. On day 50, aspartate transaminase (AST), alanine transaminase (ALT), and γ-guanosine triphosphate (γ-GTP) levels were elevated. Therefore, from day 54, we decreased the VRCZ dosage to 100 mg twice daily. After this dosage decrease, these laboratory values decreased. After starting VRCZ administration, serum CRE level was not a noticeable change (day 32; 0.37 mg/dL, day 53; 0.43 mg/dL). All *Aspergillus* antigens were negative throughout the administration period, and the (1,3)-β-D-glucan level decreased from 13.10 pg/mL on day 14 to 5.04 pg/mL on day 60. Although *Aspergillus fumigatus* grew from the pleural effusion on day 14 and the empyema on day 25, the culture was negative after combination therapy. On day 39, her body temperature and serum CRP level was 36.4 °C and 1.9 mg/dL, respectively, and the disappearance of the fungus ball was confirmed by CT images after four intrathoracic injections (Fig. 1, D).

This patient was suspected to have underlying diseases that required continued immunosuppression, and radical surgery was also impossible due to poor residual lung function. We have determined that the empyema condition has improved, therefore, we decided to perform fenestration surgery on day 64. The combination therapy with intravenous and intrathoracic administration was continued at a fixed intrathoracic dose of 200 mg until the fenestration surgery. Intrathoracic administration was performed 14 times over 36 days from day 27 to day 62. On day 71, the intravenous administration was discontinued and oral administration was started at a dosage of 150 mg twice daily. After fenestration surgery, we performed wound closure using biological tissue adhesive and negative-pressure wound therapy. Her condition improved and she was discharged on day 143 (Fig. 2). After the start of VRCZ administration, photophobia and blurred vision transiently developed, but no other ocular symptoms appeared during the treatment course.

The plasma for the VRCZ concentration measurement was sampled within 1 h before the intravenous administration. The pleural effusion samples were pooled in the chest drainage bag and collected 6–8 hours after the intravenous administration. The plasma and pleural effusion concentrations of VRCZ were measured by high-performance liquid chromatography with minor modifications of the method of Pennck et al. [10]. The analytical column was CAPCELL PAK C18 MG, 5μm, 250 × 4.6 mm (Osaka Soda, Japan), and the ultraviolet wavelength for voriconazole was 257 nm. Itraconazole was selected as the internal standard (IS).

3. Discussion

We report the successful treatment of *Aspergillus* empyema by combined intrathoracic and intravenous administration of VRCZ with therapeutic drug monitoring. In this case, the penetration ratio of VRCZ from the plasma to the pleural fluid was about 53%. Stern et al. [9] reported a penetration ratio of VRCZ at the trough level of 86%–95%. In addition, Matsuda et al. [7] reported a penetration ratio at the trough level of 19%–23% with chest tube drainage and 70%–75% without drainage. Thus, the pleural effusion penetration ratio with chest tube drainage in our case was comparable to that reported by Matsuda et al. [7].

To date, amphotericin B has been used for intrathoracic administration [4,11] In the present case, we selected VRCZ, which had already been intravenously administered. There is no report on the combined intravenous and intrathoracic administration of

VRCZ. We decided the dissolution volume of VRCZ for intrathoracic administration to 50–100 mL of saline and clamp time to about 5 hours, with reference to other reports [12,13]. After confirming the change in the plasma concentration after a single intrathoracic administration, we found that the VRCZ plasma concentration increased by about 17% after 24 h but had decreased to the pre-intrathoracic administration level 48 h later. Therefore, we considered intrathoracic administration at 48-h intervals to be feasible.

VRCZ exhibits nonlinear pharmacokinetics and has been linked to adverse effects such as liver and ocular disorders due to an unexpectedly rapid rise in plasma concentration [14]. In this case, when the daily dose of VRCZ is 300 mg or less, the VRCZ plasma trough concentration was between 0.84 and 2.73 μg/mL. However, the plasma trough concentration nonlinearly rose to 5.63 μg/mL as the intravenous dose was increased to 400 mg/day, and AST, ALT, and γ-GTP levels rose. Subsequently, when the intravenous dose was decreased, the plasma concentration also decreased, and these laboratory values fell to within the reference range. During this period, the intrathoracic administration was continued. The pleural effusion concentration of VRCZ after intrathoracic administration was 135.97 μg/mL (day 35), which was expected for sufficient local exposure. On the other hand, to avoid side effects such as liver injury and renal dysfunction, we carefully monitored the laboratory data, but none were found.

Ko et al. [4] reported the efficacy of treatment for fungal empyema in 67 patients; 4 of 9 patients with empyema caused by *Aspergillus* sp. who were administered antifungal drugs into the thoracic cavity survived. Therefore, our results may suggest that intrathoracic administration is a potential therapeutic strategy, as long as it is performed with careful monitoring of the VRCZ concentration.

One limitation of this study is that we could not obtain the plasma and pleural effusion concentrations of VRCZ at the same time. Although the results were obtained from a single case, our findings nonetheless suggest that combined intrathoracic and intravenous administration of VRCZ may be an option for the treatment of *Aspergillus* empyema.

Declaration of Competing Interest

None.

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References

[1] Ashizawa N, Nakamura S, Ide S, Tashiro M, Takazono T, Imamura Y, et al. Successful treatment of aspergillus empyema using open window thoracostomy salvage treatment and the local administration of an antifungal agent. Intern Med (Tokyo, Japan) 2016;55:2093–9.
[2] Shirakusa T, Ueda H, Saito T, Matsuba K, Kouno J, Hirota N. Surgical treatment of pulmonary aspergilloma and aspergillus empyema. Ann Thorac Surg 1989;48:779–82.
[3] Bonatti H, Lass-Floerl C, Angerer K, Singh N, Lechner M, Stelzmueller I, et al. Successful management of postpneumonectomy aspergillus pleural empyema by combined surgical and anti-fungal treatment with voriconazole and caspofungin. Mycoses 2010;53:448–54.
[4] Ko S-C, Chen K-Y, Hsueh P-R, Luh K-T, Yang P-C. Fungal empyema thoracis. Chest 2000;117:1672–8.
[5] Patterson TF, Thompson 3rd GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis: Offic Publ Infect Dis Soc Ame 2016;63:e1–60.
[6] Matsumoto K, Abematsu K, Shigemi A, Kanazawa N, Watanabe E, Yokoyama Y, et al. Therapeutic drug monitoring of voriconazole in Japanese patients: analysis based on clinical practice data. J Chemother (Florence, Italy) 2016;28:198–202.
[7] Matsuda T, Koreeda Y, Mataki H, Taira T, Noma S, Higashimoto I. A case of aspergillus empyema successfully treated with combination therapy of voriconazole and micafungin: excellent penetration of voriconazole and micafungin into pleural fluid. Intern Med (Tokyo, Japan) 2010;49:1163–9.
[8] Poupelin JC, Philit F, Richard JC, Badet M, Lemasson S, Bayle F, et al. Pericardial and pleural diffusion of voriconazole during disseminated invasive aspergillosis: report of a case with successful outcome. Intensive Care Med 2006;32:939–40.
[9] Stern JB, Girard P, Caliandro R. Pleural diffusion of voriconazole in a patient with aspergillus fumigatus empyema thoracis. Antimicrob Agents Chemother 2004;48. 1065–65.
[10] Pennick GJ, Clark M, Sutton DA, Rinaldi MG. Development and validation of a high-performance liquid chromatography assay for voriconazole. Antimicrob Agents Chemother 2003;47:2348–50.
[11] Chung HC, Chang J, Ahn CM, Kim SK, Lee WY, Lee DY. Pleural aspergillosis. Yonsei Med J 1988;29:84–8.
[12] Dusemund F, Weber MD, Nagel W, Schneider T, Brutsche MH, Schoch OD. Characteristics of medically and surgically treated empyema patients: a retrospective cohort study. Respir Int Rev Thorac Dis 2013;86:288–94.
[13] Ueno T, Toyooka S, Soh J, Miyoshi K, Sugimoto S, Yamane M, et al. Intrathoracic irrigation with arbekacin for methicillin-resistant staphylococcus aureus empyema following lung resection. Interact Cardiovasc Thorac Surg 2012;15:437–41.
[14] Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother 2002;46:2546–53.