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Case Report

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Breakthrough mucormycosis In two cases of hematological malignancies successfully treated with amphotericin B colloidal dispersion

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Abstract

Background: *Patients with hematologic malignancies have poor immunity, and they are more vulnerable to fungal invasion because of disease characteristics and clinical treatment such as chemotherapy. Mucor infections in hematologic malignancies are rare, but once occurred usually lead to high mortality.*

In this study, we report two cases of hematologic malignancies complicated with breakthrough mucormycosis (BT-MCR), which were treated with amphotericin B colloidal dispersion (ABCD) combined with or without other antifungal agents.

Case Presentation: *Case 1 shows a patient with natural killer cell leukemia, type 2 diabetes, and graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (allo-HSCT). This patient was admitted to the First Affiliated Hospital of Soochow University because of fever with cough and expectoration for a week. Next-generation sequencing (NGS) of alveolar lavage fluid revealed that the patient was infected with Rhizomucor pusillus and Enterococcus faecalis.*

This patient was infected with fungi although he had taken voriconazole for prevention. Considering the renal toxicity of amphotericin B deoxycholate, the patient received ABCD via intravenous drip combined with posaconazole via oral administration for Rhizomucor pusillus infection and meropenem via intravenous drip for Enterococcus faecalis infection during 45 days of treatment. The patient was free of complaints in the next 2-month follow-up. Case 2 represents a patient with acute myeloid leukemia. During induction chemotherapy, the patient presented with weakness of the left limbs, and head MRI showed multiple cerebral infarctions (MCI). In addition, he had high fever with right-face swelling and pain, and the NGS of blood revealed that he had Mucor circinelloides and Stenotrophomonas maltophilia infection. ABCD and ceftazidime/avibactam were administered to the patients via intravenous drip. The patient also achieved complete remission after later consolidation chemotherapy and successfully underwent allo-HSCT.

Conclusion: *ABCD shows great efficiency with or without other antifungal agents in treating hematological malignancies complicated with BT-MCR. Despite its infusion-related adverse effects and nephrotoxicity, ABCD shows great application potential for patients with hematologic malignancies, who are often more susceptible to fatal BT-MCR. Furthermore, more valid data should be collected on the combination therapy (ABCD and posaconazole).*

Keywords: Breakthrough Mucormycosis, Amphotericin B Colloidal Dispersion, Hematological Malignancies, Allogeneic Hematopoietic Stem Cell Transplantation, Antifungal Therapy.

Introduction

As an invasive fungal disease, mucormycosis is difficult to diagnose and easy to progress; therefore, it has high mortality and deserves urgent surgical or medical intervention [1]. Mucormycosis is rare; thus, few studies have focused on its incidence, and no valid incidence rates are found because of the impossibility of conducting large, randomized clinical trials [2]. The epidemiology of mucormycosis differs among countries. In Europe, Rhizopus

spp. (34%) and Mucor spp. (19%) are the most common species in patients with mucormycosis [3].

Moreover, hematological malignancies and transplantation, as common underlying diseases of mucormycosis, are of considerable significance. As well as hematological malignancies and transplantation, diabetes mellitus is another point [4]. In a global review, underlying hematological malignancy was found to be associated with disseminated mucormycosis (OR 4.20; 95% CI 1.68–10.46; P = 0.002) [6].

In addition, Mucorales is the common causative agent in patients with hematological malignancies and HSCT other than Aspergillus[5].

Under normal conditions, antifungal prophylaxis or treatment is performed against Aspergillus in immunocompromised transplant recipients using voriconazole and echinocandins as the first treatment option. Selective pressure from prolonged use of voriconazole may explain the increased incidence of mucormycosis among patients at high risk for invasive fungal infections [7]. This type of mucormycosis is known as breakthrough mucormycosis (BT-MCR).

Early diagnosis of mucormycosis will considerably improve prognosis because of its progressivity. For diagnosis, these measures must be considered. For example, attention should be given to patients with risk factors associated with clinical and imaging manifestations.

Diagnostic methods for histopathology, cultures, and advanced molecular techniques are necessary [4]. According to the most potent agents in vitro, amphotericin B (AmB), posaconazole and isavuconazole became the treatment of choice for mucormycosis. Based on the ECIL-6 guidelines, the best recommendation is the combination of antifungal therapy, surgical intervention, and effective control of underlying diseases.

In antifungal monotherapy, amphotericin B colloidal dispersion (ABCD) is recommended for first-line treatment of mucormycosis with recommended-grade CII [9]. However, limited data could be used to guide antifungal combination therapy [1].

Considering that mucormycosis is rare and progressive, in this study, we describe two cases of mucormycosis in hematological malignancies successfully treated with ABCD in combination with other antifungal agents. In our patients, Rhizomucor pusillus belongs to Rhizopus spp., whereas Mucor circinelloides belongs to Mucor spp.

Case Presentations

Case 1

A 37-year-old man with diabetes was diagnosed with natural killer cell leukemia at the First Affiliated Hospital of Soochow University in January 2020. After several courses of chemotherapy, he achieved a complete remission and favorably received allo-HSCT. However, he quickly developed symptoms of graft-versus-host disease (GVHD) of the skin, liver, and lungs. Subsequently, he received ruxolitinib 5 mg b.i.d. per o.s. During immunosuppression, oral voriconazole (4 mg/kg) every 12 hours was continuously used to prevent fungal infection. However, this patient presented with fever, cough, and bloody sputum for a week and presented to the First Affiliated Hospital of Soochow University for further treatment. His chest computed tomography (CT) on June 15 (Figure 1A) revealed a cavity in the upper lobe of the right lung, indicating infectious lesion.

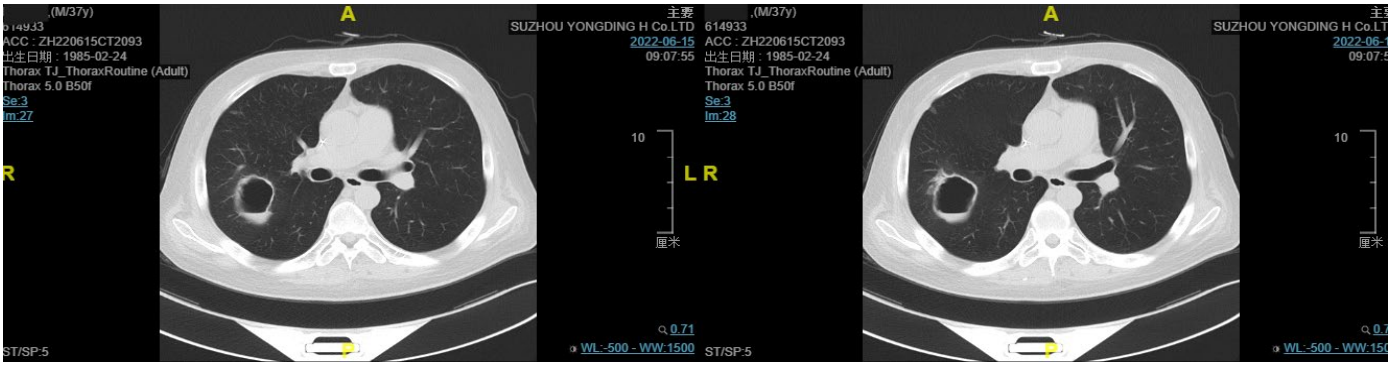

Figure 1A: Coronal chest computed tomography (CT) of the patient. A) On June 15, CT revealed a cavity in the upper lobe of the right lung.

We continuously used oral voriconazole for 5 days with no improvement in his condition. In confirming the pathogens for precision medication, we conducted an alveolar lavage and took the alveolar lavage fluid to next-generation sequencing (NGS; Table 1A). The results showed that the fungus detected was Rhizomucor pusillus, and the bacterium detected was Enterococcus faecalis.

Case 1	Species	The Number of Sequences Detected
Fungus Detected	Rhizomucor Pusillus	865
Bacterium Detected	Enterococcus Faecalis	6009

Table 1A: Results of the next-generation sequencing of alveolar lavage fluid. Rhizomucor pusillus and Enterococcus faecalis were the main causative agents.

Based on the results, medications were adjusted to increasing doses of intravenous ABCD (initial dose of 1 mg/kg and increased by 1 mg/kg every 5 days until 3 mg/kg) every day complicated with oral posaconazole (8 mg/kg), every 12 hours, and intravenous meropenem (0.5 g) every 8 hours. After a total of 45 days of treatment (with a cumulative dose of 6000 mg for ABCD), his symptoms were considerably improved, and chest CT reexamination every 15 days described the gradual shrinkage of the cavity (Figures 1B,C).

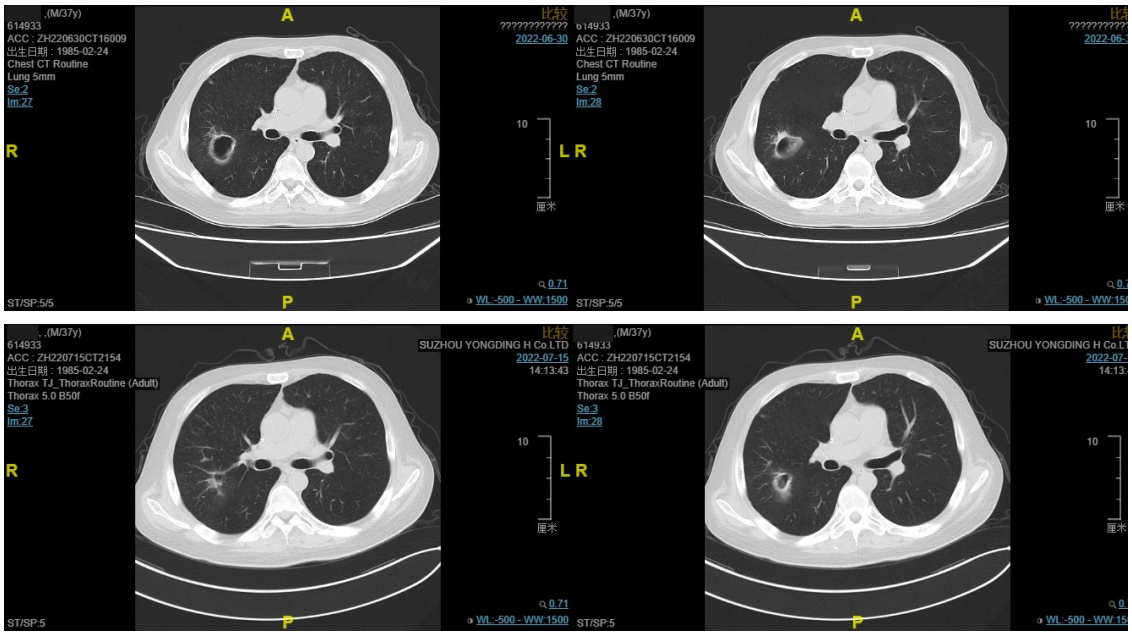

Figure 1B&C: B) On July 1, the shape of the cavity was smaller than previously recorded. C) On July 15, the cavity became smaller, showing a state of improvement in lesion absorption and treatment efficiency.

Case 2

In September of 2021, a 23-year-old man presented to the First Affiliated Hospital of Soochow University with malaise for half month and progressive lower extremity edema. After completing relevant inspections, the patient was newly diagnosed with acute myeloid leukemia (AML) and promptly started induction chemotherapy of VEN + HA (venetoclax plus homoharringtonine and cytarabine) combined with the continuous use of oral voriconazole (4 mg/kg) every 12 hours to prevent fungal infection.

However, during chemotherapy, the patient presented with multiple cerebral infarctions (MCI), maxillary sinus, ethmoid sinus, and sphenoid sinusitis. Moreover, during bone marrow depletion, he presented with high fever with facial swelling and pain. With regard to facial features, he presented with swelling and protrusion of the right eye, drooping eyelids, and facial edema. Intravenous piperacillin/tazobactam and oral voriconazole were ineffective.

Tissue biopsy was not made. Before his infection progressed to a necrotic ulcer or more seriously rhino-(facial)orbital-cerebral mycosis, complete NGS of blood Table 1B revealed that his main pathogens included Mucor circinelloides and Stenotrophomonas maltophilia. He received intravenous ABCD (initial dose of 1 mg/kg and increased by 1 mg/kg every 3 days until 3 mg/kg) every day and ceftazidime/avibactam (2.5 g) every 8 hours against these two pathogenic agents.

Case 2	Species	The Number of Sequences Detected
Fungus Detected	Mucor Circinelloides	8850
Bacterium Detected	Stenotrophomonas Maltophilia	2810

Table 1B: Results of the next-generation sequencing of alveolar lavage fluid. Mucor circinelloides and Stenotrophomonas maltophilia were the main causative agents.

After 15 days of ABCD use, the lesion was healed along with the recovery of the patient from mucormycosis. He subsequently received two cycles of chemotherapy with ID-AraC (1.0 g/m2 every 12 hours). After the assessment of MRD-negative complete remission, he underwent haploid HSCT from his father successfully.

Discussions

Case 1 described a patient with natural killer T-cell leukemia who had GVHD and was diagnosed with invasive pulmonary mucormycosis. However, a history of prior prophylaxis or treatment against Aspergillus instead of Mucorales with voriconazole should result in a higher possibility of invasive pulmonary mucormycosis [3].

This patient was in an immunosuppressed state, thereby promoting the progression of mucormycosis. Different from Aspergillus and other types of airborne opportunistic fungi, Mucorales are acute and angioinvasive with a wider host range and qualitative and/or quantitative defects in phagocytes [9]. Pulmonary mucormycosis is characterized by refractory fever with broad-spectrum antibiotics, dry cough, progressive dyspnea, and pleuritic chest pain. Notably, infection tends to cross tissue planes and vessels within the lung, which leads to necrosis of the surrounding parenchyma, thereby causing pulmonary cancerous cavity or potentially fatal hemoptysis [10].

Evidently, mucormycosis has broken through the lung tissue and blood vessels and formed a cavity, which causes patient's bloody sputum. Common radiographic and pathologic findings of invasive pulmonary infection include nodules, lobar infiltrates, wedge-shaped infarction, and cavitary lesions [11].

Moreover, the reverse halo sign (the lesion surrounded by a ground glass appearance) on chest CT has certain significance in pulmonary filamentous mycosis, particularly Mucor infection, and it can also be used as a clinical diagnostic criterion for non-Aspergillus filamentous mycosis [12].We still performed fiberoptic bronchoscopy, which revealed only infectious lesions in the bronchus, and the final answer given to us was the NGS results of the patient's bronchoalveolar lavage fluid. For pulmonary mucormycosis, despite the absence of public consensus treatment guidelines, the recommended antifungal therapy includes conventional AmB with a maximum tolerated dose of 1.0–1.5 mg/kg/day or oral posaconazole (800 mg daily in four divided doses).

Considering that the patient's renal function was defective, and AmB can cause renal injury, we promptly selected ABCD for its less nephrotoxicity [9]. Meanwhile, although we have not been able to query relevant documents and experiments of joint ABCD and posaconazole, we adopted this two-drug combination regimen as an innovation.

Under treatment with this regimen, the patient's creatinine level did not increase significantly Figure 2A. To our knowledge, given that the two-drug combination has not been reported, we used this regimen innovatively, and it achieved a good therapeutic effect.

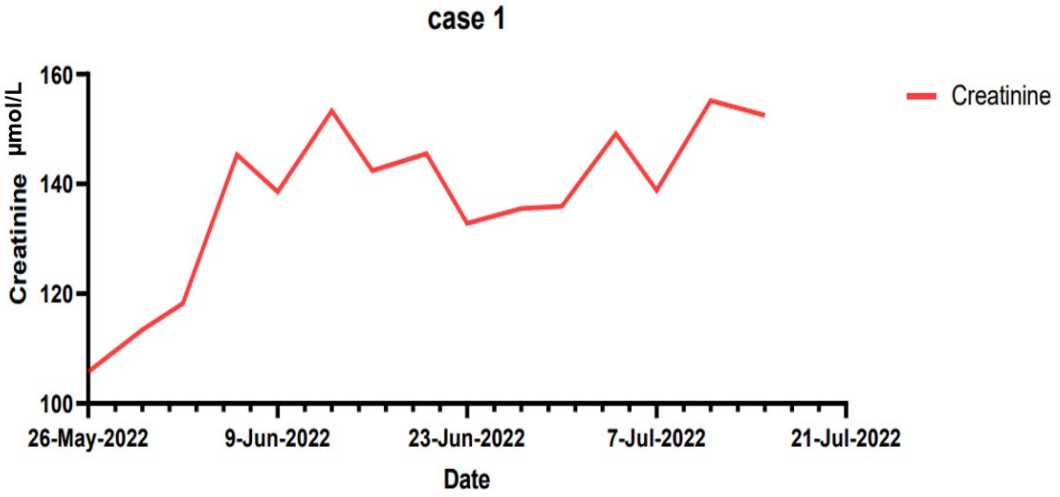

Figure 2A: Creatinine value of the patients during hospitalization. A) The patient's creatinine level was high but did not increase significantly.

In case 2, different to case 1, we used posaconazole before ABCD; however, the effect was not significant. Finally, we adjusted to a single fungal drug regimen for ABCD combined with other antibacterial drugs based on the NGS results. Patient's temperature was controlled and maintained within the normal range after 6 days of repeated fluctuations. Based on previous reports, ABCD had no net adverse effects on renal function [13].

With regular biochemical testing, the patient's creatinine level remained within the normal range throughout the treatment (Figure 2B). Thereafter, he received two cycles of ID-AraC chemotherapy regimen, and his assessments showed complete response and negative MRD. On January 20, 2022, modified BU/CY conditioning was completed.

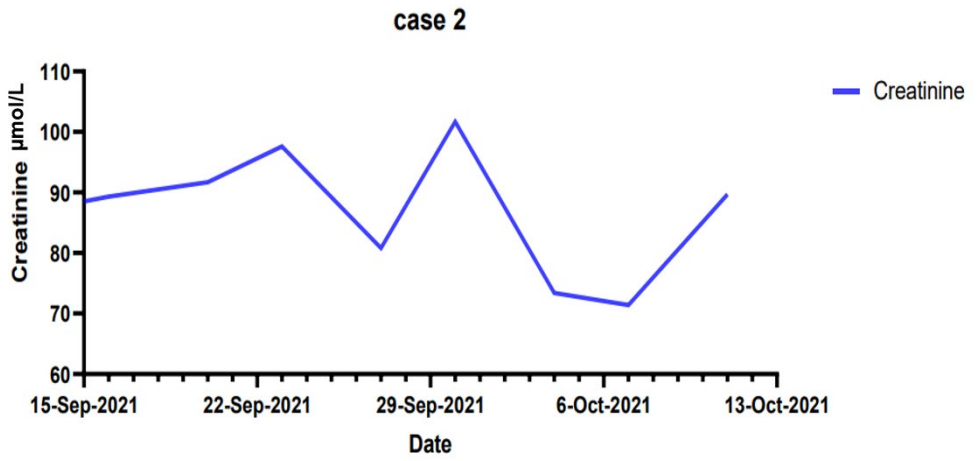

Figure 2B: Creatinine value of the patients during hospitalization. The patient's creatinine level remained within the normal range.

On January 28, haploidentical HSCT from father to son was performed, and infusion and hematopoietic reconstruction after transplantation were conducted smoothly. Based on this case, monotherapy with ABCD was also feasible.

In patients with hematologic malignancies and HSCT, aggressive mucormycosis has a mortality rate of 80% [12]. In addition, BT-MCR not only can attack immunocompromised people on voriconazole but also can occur on Mucorales-active antifungals [14]. For treatment, single drugs combined with other antifungal drugs are feasible.

The regimen of AmB combined with posaconazole was frequently analyzed. In the research by Schwarz et al. [8] regardless of the species, interactions were similar to most of the tested isolates. Nevertheless, Wagner et al, found that the most active drug for Mucor circinelloides was AmB and posaconazole, with MIC50 values of 0.125 and 0.5 mg/L, respectively. Similar results were obtained for Rhizomucor pusillus [15].

We innovatively tried the combination of ABCD and posaconazole and achieved excellent patient outcomes. For invasive pulmonary mucormycosis, the combination of medical antifungal therapy and early surgical resection is a feasible and effective strategy. Surgical resection significantly increases survival, and it should be strongly considered for patients with pulmonary mucormycosis [16].

However, some experts believe that surgical intervention is not necessary. Gumral et al reported that in pulmonary cases, only antifungal therapy without surgery had been accepted in general [17]. After comparison between ABCD and other types of antifungal drugs, we selected ABCD. Hamill found that differences worked in ABCD's favor. ABCD (patients with hematological malignancies and pulmonary disease but not sinus infections) was significantly better for most categories and sites [18]. In a randomized, double-blind, multicenter trial comparing ABCD with AmB, ABCD showed the same efficacy and higher renal safety in the treatment of invasive Aspergillosis. However, patients who received ABCD likely have infusion-related chills and fever than those who received AmB Should be [19,20].

Adverse events leading to discontinuation included chills, fever, and hypotension, which may be related to ABCD infusion or underlying infection. In vitro and in vivo studies have shown that the physical form of ABCD does not reduce its efficacy [13]. For infusion reactions, prophylaxis can be used as follows: 1–5 mg of dexamethasone 20–30 min before infusion or pretreatment with additional antihistamines (such as 25 mg of promethazine and 20–40 mg of diphenhydramine). For preventing the occurrence of adverse effects, acetaminophen can be administered orally or diphenhydramine (25–50 mg for adults) intravenously to treat drug-induced fever, chills, and headaches. In addition, experimental injection or slow infusion rate is necessary. Diuretic, hydration, alkalizing urine, and promoting drug drainage can be applied to reduce renal injury. In severe cases, calcium channel retarder and selective polypamine A receptor activator can be used for treatment [21].

The use of low doses of AmB and the avoidance of the combined use of aminoglycoside antibiotics or cyclosporine can reduce the risk of nephrotoxicity. Blood routine and liver and kidney function were monitored during treatment [22].Therefore, closely monitoring the change in blood potassium concentration and observing the symptoms of fatigue and abdominal distension simultaneously are recommended.

Conclusion

Systemic infections caused by Mucor spp. have been reported in immunocompromised patients because of hematological malignancies or uncontrolled diabetes. BT-MCR is diagnosed while a patient is receiving antifungal medications, most commonly voriconazole.

We successfully treated two patients with BT-MCR with ABCD and combined ABCD and posaconazole. Both patients showed long-term complete remission prognosis. The pharmacological mechanism of ABCD is similar to that of AmB, and it has better renal safety and lower incidence of hypokalemia.

Medical staff should follow the medication guidelines and standardize the guiding drugs when using ABCD. Consequently, they can effectively prevent and control the occurrence of adverse reactions such as infusion reaction, renal toxicity, and hypokalemia. More research and valid data should be obtained and collected on the combination therapy for BT-MCR to improve agrochemical regulation.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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