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CASE REPORT

Successful Treatment of Rare Pulmonary *Coprinopsis cinerea* Infection in a 17-Year-Old Female After Hematopoietic Stem Cell Transplantation: A Case Report

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Abstract: Invasive fungal infections (IFIs) are among the most severe complications in recipients of hematopoietic stem cell transplantation (HSCT) recipients and in patients with hematological malignancies. An increasing number of uncommon fungal infections have been reported in this era of antifungal prophylaxis. *Coprinopsis cinerea* is a rare pathogen that causes opportunistic infections in the immunocompromised patients, including HSCT recipients and is associated with very high mortality rates. Herein, we present a successfully treated pediatric HSCT patient with breakthrough pulmonary IFI caused by *Coprinopsis cinerea* despite posaconazole, prophylaxis using multidisciplinary approaches.

Keywords: *Coprinopsis cinerea*, *Hormographiella aspergillata*, invasive fungal infection, hematopoietic stem cell transplantation, leukemia, case report

Introduction

Invasive fungal infections (IFIs) are among the most severe complications and contribute to high morbidity and mortality in hematopoietic stem cell transplantation (HSCT) recipients and patients with hematological malignancies.[1] Administration of high-dose chemotherapy, immunosuppressive agents, steroids, and broad-spectrum antibiotics increases the incidence of IFIs in HSCT recipients and patients with hematological disorders.[2,3] In addition, IFIs often exhibit rapid disease progression and a slow response to treatment, leading to limitations in diagnosing them and treatment delays.[3]

Although antifungal prophylaxis is recommended in most cases of HSCT, the risk of developing an IFI remains high, particularly in patients with co-existing with other complications, such as prolonged neutropenia, severe viral and bacterial infections, and graft-versus-host diseases (GVHDs).[1,2] In addition, IFIs on antifungal prophylaxis in HSCT patients often have an insidious onset, which may increase the risk of misdiagnosis and delay treatment.

Candida albicans and *Aspergillus spp*. are among the most common causative organisms of fungal infections in HSCT recipients and patients with hematological malignancies in China.[4,5] However, there is an increasing number of uncommon fungal infections, which may be associated with a shift in the etiology spectrum of IFIs due to antifungal prophylaxis.[6–8] In this paper, we report a rare case of pulmonary *Coprinopsis cinerea* (*C. cinerea*) infection in a 17-year-old patient with B-cell acute lymphoblastic leukemia (B-ALL) after HSCT.

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Case Description

A 17-year-old female with the second relapse of B-ALL received chimeric antigen T-cell (CART) salvage therapy, followed by co-transplantation of haploidentical stem cells and unrelated cord blood in September 2021. The patient had a previous disseminated pulmonary tuberculosis infection during the first relapse in July 2020. However, she recovered well after treatment with anti-tuberculosis drugs, including isoniazid (10 mg/kg/day), rifampicin (10 mg/kg/day), and levofloxacin (10 mg/kg/day) from July 2020 to April 2021, and continued to receive oral isoniazid prophylaxis until 3 days prior to HSCT. Chest computed tomography (CT) revealed no residual tuberculosis lesions and interferon-gamma (IFN-γ) release assays was negative prior to transplantation. Furthermore, there was no evidence of fungal infection during chemotherapy or prior to HSCT.

The patient received a myeloablative conditioning regimen consisting of cyclophosphamide, busulfan, fludarabine, and thiotepa without total body irradiation. The post-transplant immunosuppressants included of post-transplant cyclophosphamide, cyclosporine, and mycophenolate mofetil. In addition, oral posaconazole (200 mg every 8h) was commenced 3 days after HSCT as an antifungal prophylaxis. Additionally, neutrophils and platelets were engrafted on 15 and 24 days after transplantation, respectively. Engraftment syndrome with fever, skin rashes, and elevated bilirubin levels was observed during cell engraftment from day 14 after transplantation. However, these symptoms resolved after intravenous administration of methylprednisolone (1 mg/kg/day for 4 days from day 15 to day 18, after which the dose was tapered and discontinued on 27 days after HSCT). No other severe complications were noted.

The patient began to cough slightly from 23 days after HSCT. Since this patient had a history of tuberculosis infection, rifapentine (600 mg per week) was administered in combination with isoniazid (10 mg/kg/day) for tuberculosis prophylaxis. However, the patient showed no signs of respiratory distress, including dyspnea, tachypnea, and hypoxemia. The cough lasted five days, and the patient developed a throbbing, dull pain in the back. A chest CT was performed, and a large nodular lesion (32.02 mm × 24.77 mm × 42.73 mm) with a faint surrounding vitreous subpleural of the right upper lobe was observed (Figure 1A and B). Therefore the patient was suspected of having tuberculosis or an IFI, and a bronchoscopy was performed. Caspofungin (loading dose at 70 mg/m^2 for 1 day and then 50 mg/m^2/day) was commenced on day 27 after HSCT, and posaconazole was switched to intravenous voriconazole (loading dose at 9mg/kg, every 12h, for 1 day and then 8mg/kg, every 12h) because the patient developed a fever 4 days later. The bronchoalveolar (BAL) fluid was positive for cytomegalovirus (CMV), human herpes virus 6 (HHV-6), and *Actinomyces odontolyticus* using next-generation sequencing. However, in contrast, using the PCR-based analysis, the BAL fluid was negative for fungi and tuberculosis. In addition, bacterial and fungal cultures of the BAL fluid were negative.

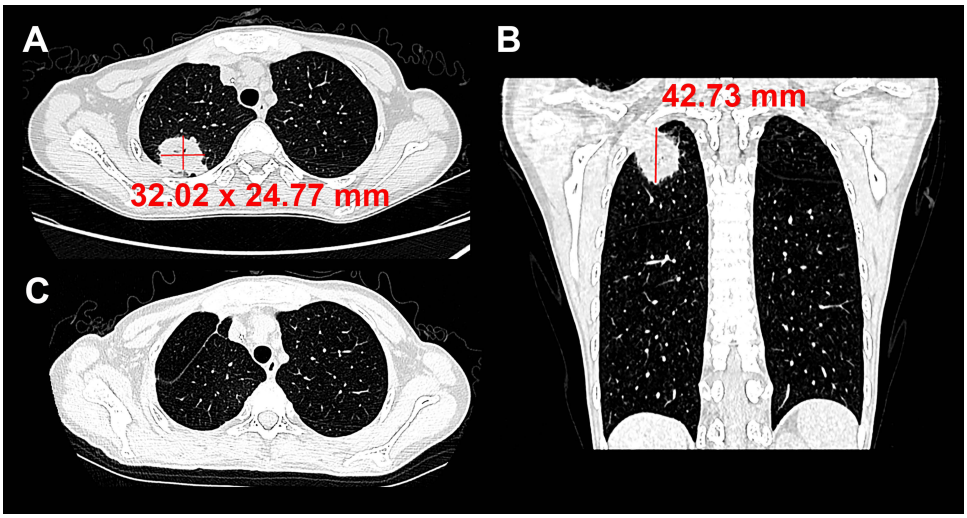

Figure 1 Chest computed tomography images of the patient before and after wedge resection of the lung lesions. Representative axial (**A**) and coronal (**B**) CT scan images revealed a large nodular lesion (32.02 mm × 24.77 mm × 42.73 mm) with a faint surrounding vitreous subpleural located in the right upper lobe. The chest CT scans show no new lung lesions 5 months after the wedge resection (**C**).

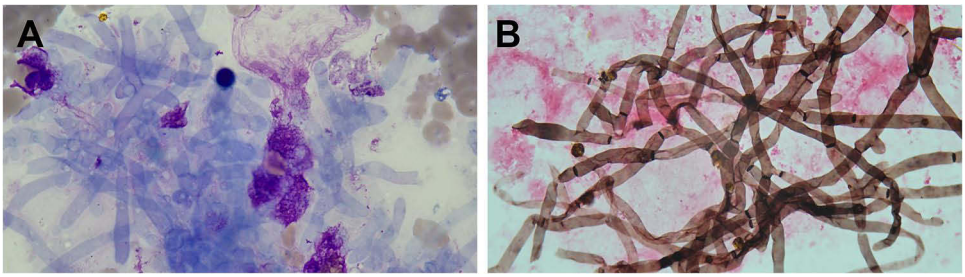

Figure 2 Histology analysis of the lung sections after the wedge resection surgery. Septate hyphae were observed by Wright-Giemsa (**A**) and hexamine-silver (**B**) staining of lung sections, indicating *C. cinerea* infection.

The antibiotics, imipenem (15mg/kg, every 6h) and high-dose penicillin (100,000 U/kg, every 6 h) were administered to treat Actinomyces infections for 2 months. Ganciclovir (5 mg/kg, every 12h) was also commenced for antiviral treatment. Despite the above treatment, the patient began to have hemoptysis, and a reassessment of the chest CT showed that the lung lesion was unresolved. Therefore, a wedge resection of the lung lesion was performed because the lesion was still localized. The next-generation sequencing analysis of the lung tissue revealed *C. cinerea* infection (NCBI accession PRJNA938261). This was later confirmed when septate hyphae were observed by both Wright-Giemsa and hexamine-silver staining of lung sections, indicative of C. cinerea infection (Figure 2). Therefore, antifungal treatment was switched to amphotericin B (starting from 0.1 mg/kg/day then gradually increased to 0.7 mg/kg/day) for 2 weeks, followed by oral voriconazole as follow-up therapy. Chest CT scans showed no new lung lesions 5 months after the wedge resection surgery (Figure 1C).

Discussion

C. cinerea, or normally seen in its asexual form *Hormographiella aspergillata* (*H. aspergillata*), is an environmental mold that rarely causes human infection.[9] In recent years, the administration of antifungal prophylaxis has reduced the incidence of IFIs in HSCT patients or those with hematological malignancies. However, this may cause a shift in the spectrum of IFI etiology and increase the risk of occasional fungal infections, including *C. cinerea*.[3,10,11] This paper reports a rare pediatric/adolescent case of a patient with recurrent B-ALL who developed a breakthrough *C. cinerea* infection after HSCT, despite antifungal prophylaxis with posaconazole.

The diagnosis of C. cinerea infection is challenging because patients often lack the typical symptoms. C. cinerea infection is primarily responsible for pulmonary infections. However, *C. cinerea* infections involving the skin, heart, intestine, central nervous system, and eyes have also been reported. In a very few cases, systemic C. cinerea infection involving multiple organs have been reported, with very high mortality rates despite intensive treatment.[12–16] *C. cinerea* infections are more frequently observed in the immunocompromised patients. However, a few cases of C. cinerea infection have also been observed in the immunocompetent patients, particularly those who undergoing invasive procedures, such as cardiovascular and ophthalmic surgeries.[17,18]

Fungal cultures to identify the filamentous basidiomycetes directly under a microscope remains the key finding for the diagnosing *C. cinerea* infections. *C. cinerea* grows in various media without cycloheximide at 25 °C or 35 °C.[14] However, the sensitivity of fungal cultures is low and requires experienced technicians to differentiate them from other fungal species and avoid misdiagnosis.[19] Conventional serological methods, including galactomannan and β-D-glucan, cannot be detected in most patients infected with C. cinerea. However, a recent study from France suggested that galactomannan and β-D-glucan could be detected in the culture media of *H. aspergillata* isolated from two patients, suggesting that these assays may provide additional clues in patients suspected of having an IFI.[6] A more reliable method for diagnosing *C. cinerea* infections is to use molecular techniques such as PCR-based sequencing and other next-generation sequencing methods.[16,20,21] These techniques can efficiently analyze a broad spectrum of pathogens, but their sensitivity varies between sample types. In line with previously reported cases in adult patients, we observed that molecular diagnostic methods might have higher sensitivity in lung tissue than in the BAL fluid.[6] Thus, a biopsy of the

lung lesions may be considered for early diagnosis in future patients as has been recommended in some centers for adult patients.

The efficacy of antiviral drugs varies from person to person. Susceptibility breakpoints may provide a rationale for the use of specific antifungal medications. However, there are no current standard guidelines for interpreting minimum inhibitory concentration (MIC) breakpoints for *C. cinerea* or *H. aspergillata* from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI) guidelines.[19] In addition, strains of *C. cinerea* resistant to various antifungal agents, including azoles, echinocandins, and amphotericin B, have been reported in different institutions.[9,13,22,23] Echinocandins, such as caspofungin and micafungin, may not be recommended as a treatment options, probably because of the high MICs in many of the reported cases.[10,14,24,25] Fluconazole, flucytosine, and itraconazole have also been reported to have high MICs. Although low MIC values of posaconazole have been reported in some cases, in the present case the patient developed a breakthrough infection despite posaconazole prophylaxis.[26] Hence, amphotericin B and voriconazole may be the treatment of choice because of their low MICs in most reported cases. In the present case, amphotericin B was administered after for 2 weeks after surgical resection of the lung lesion, followed by oral maintenance with voriconazole. No relapse of the fungal infection was observed during the follow-up period. Unfortunately, susceptibility tests were not performed on this patient because we could not isolate the mold from the culture.

Due to the uncertainty of the outcomes of antifungal therapy, surgery may be used as a complementary tool to remove localized lesions, particularly in patients with pulmonary IFI.[27] In addition, surgical resection in combination with antifungal medications may contribute to a more favorable outcome as this strategy has successfully treated a few cases of invasive *C. cinerea* infection.[28] However, it is difficult to conclude the effectiveness of this strategy at this time because such cases have only been reported in a small series.

In summary, administering antifungal drugs for prophylaxis has greatly reduced the incidence of common fungal infections in HSCT recipients and patients with hematologic malignancies. However, there has been a simultaneous increase in the incidence of uncommon fungal infections that have made the management of these patients challenging in recent years. Molecular techniques play key roles in diagnosing these rare fungal infections; however, the sensitivities of different sample types should be considered. Therefore, performing direct biopsies of infected lesions is ideal for better sensitivity. Furthermore, multiple lines of antifungal drugs should be considered when looking medication with optimal efficacy, as most of these cases have been reported in a small number of patients. Hence, combined antifungal medication and surgical approach may be considered to increase patient survival in patients with localized pulmonary lesions. Nevertheless, prompt diagnosis and intervention are key to optimal prognosis for patients with rare fungal infections including *C. cinerea* infections.

Ethical Approval and Consent for Participate

Written consents in approval for publication of this manuscript were obtained from both the patients and parents. The publication of this case report has been approved by Shenzhen Children's Hospital Ethics Committee (approval number 2021102).

Consent for Publication

Written consent was obtained from the parents of the patient for the participation of this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflict of interests to declare for this work.

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