CASE REPORT

Disseminated *Cunninghamella bertholletiae* Infection During Induction Chemotherapy in a Girl with High-Risk Acute Lymphoblastic Leukemia


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Invasive fungal infections in children with acute lymphoblastic leukemia have been a major cause of mortality. Recent reports have described increasing incidence of invasive non-*Aspergillus* mold infections in patients with hematological malignancies. It is always challenging to treat invasive fungal infection and underlying hematological malignancies successfully. Here we report a girl with high-risk acute lymphoblastic leukemia who developed disseminated *Cunninghamella bertholletiae* infection during induction chemotherapy. This case illustrates the difficulties of diagnosis and treatment of invasive *C. bertholletiae* infection. It also highlights the necessity for physicians to keep high suspicion and awareness for this infrequent fungal infection.

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1. Introduction

Invasive fungal infections are serious and often fatal complications in immunocompromised patients, especially those with hematological malignancy. The diagnosis and antifungal treatment among these patients are often delayed because of a lack of specific clinical and radiological features. The incidence of invasive fungal infections in children with cancer is around 4.9–7.2%, and the mortality is about 21.7–59%. Cunninghamella bertholletiae is a rarely reported species of invasive fungal infection and the lung is the most commonly involved organ. In pediatric patients, it causes rapid progression and therefore a high mortality rate. Here we present a patient with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) who developed invasive C. bertholletiae infection during induction chemotherapy. This case illustrates the difficulties of diagnosis and treatment of invasive C. bertholletiae infection. It also highlights the necessity for physicians to keep high suspicion and awareness for this infrequent fungal infection.

2. Case report

A 13-year-old girl presented with hyperleukocytosis (leukocyte count 135.8 \(\times\) 10⁹ cells/L with 91% blasts) and was diagnosed as Ph+ ALL in October 2010. She received chemotherapy according to the Taiwan Pediatric Oncology Group (TPOG) 2002-ALL-VHR protocol. The leukocyte count was < 1 \(\times\) 10⁹ cells/L on Day 8. Antifungal prophylaxis with fluconazole was used from then onwards. She also received routine Pneumocystis jiroveci pneumonia prophylaxis with cotrimoxazole according to the TPOG protocol.

She developed cough, occasional hemoptysis, and dyspnea on Day 23. Chest radiography revealed a nodule over the left upper lobe. She was started on voriconazole. Computed tomography (CT) of chest and abdomen showed mixed nodularity and groundglass appearance (halo sign) at left upper lobe (Figure 1A), and a hypodense lesion at the spleen with adjacent soft tissue edema (Figure 1B). These findings were suggestive of invasive fungal infection, particularly invasive aspergillosis. Chemotherapy was discontinued and a granulocyte-stimulating factor was given.

![Figure 1](image_url)
Chest radiography showed diffuse consolidation over the left lung as well as massive pleural effusion in 1 week. She also had progressive incoherent speech and tremor. Magnetic resonance imaging of brain showed a small round lesion with post contrast ring enhancement suggestive of brain abscess (Figure 1C). Serum galactomannan test was negative. Her general condition improved gradually after the leukocyte count was elevated. Consolidation and pleural effusion at the left lung was persistent in the series of chest radiographs. The bone marrow examination after incomplete induction chemotherapy showed ALL in morphological remission. Further intensive chemotherapy was withheld, and she took imatinib for treatment of Ph+ ALL.

About 6 weeks later, a follow-up CT scan of the whole body showed necrotizing pneumonia with empyema at the left upper lung. In addition to the stationary splenic lesion and brain abscess, abscess at the left thigh was found (Figure 1D). The patient underwent surgical intervention with decortication and wedge resection of the lung. The histology examination revealed extensive necrosis with a small focal area of invasive fungal disease. Microbiologic examinations showed broad and nonseptated hyphae, suggesting mucormycosis rather than aspergillosis (Figure 2). The fungal culture was negative. In order to elucidate the causative organism, we extracted the DNA from the lung biopsy specimen and amplified the sequences by polymerase chain reaction. The amplified sequences matched C. bertholletiae. Voriconazole was immediately substituted by amphotericin-B deoxycholate (AmB). Unfortunately, a frank relapse of ALL occurred soon after C. bertholletiae infection was diagnosed. She received re-induction chemotherapy concomitantly with AmB. She developed pancytopenia and septic shock 2 weeks after re-induction chemotherapy. She was transferred to the pediatric intensive care unit. Disseminated intravascular coagulopathy occurred and resulted in massive gastrointestinal bleeding and multifocal intracranial hemorrhages. Owing to the poor prognosis, the decision to withdraw life-sustaining treatment was made in close discussion with her parents. She died on the following day.

3. Discussion

The incidence of mucormycosis (formerly zygomycetes) infections in immunocompromised patients has been increasing during the past 2 decades. The annual incidence of mucormycosis increased with age from 0.3/million in children aged 0–9 years to 3.9/million in patients aged > 89 years. The most common types of infection were sinus (39%), pulmonary (24%), and cutaneous (19%). Dissemination developed in 23% of cases. Various environmental factors such as use of more potent immunosuppressive therapy and some antifungal agents probably account for the increasing incidence. Rhizopus is the most common genus causing human mucormycetes infections, followed by genera such as Mucor and Lichtheimia, accounting for 70–80% of all mucormycosis cases. By contrast, Cunninghamhamella, Apophysomyces, Saksenaea, Rhizomucor, Cokeromyces, Actinomucor, and Syncephalas-trum species are individually responsible for < 1–5% of reported cases of mucormycosis. The diagnosis of mucormycosis is difficult. Despite the availability of modern methods (e.g., tissue polymerase chain reaction), about 10% of patients were diagnosed post mortem or during the last 24 hours prior to death. The mortality rate is usually high (around 50%).

Among the major mucormycete species, C. bertholletiae is especially difficult to treat, and the overall mortality rate is up to 77%. In an animal study, C. bertholletiae infection demonstrated greater virulence (higher sporangiospore germination rate and hyphal metabolic activity) than other mucormycete species. C. bertholletiae also exhibited increased resistance to human neutrophil-induced hyphal damage and is more capable of suppressing release of IL-8 as compared to other mucormycete species. To our knowledge, only 12 children with C. bertholletiae infection have been reported, four of whom (33%) had disseminated infection. Only one child with disseminated infection survived.

It is not easy to distinguish mucormycosis and aspergillosis clinically as illustrated in our patient. The pathophysiology, mode of acquisition, and underlying patient risk factors are similar between the two entities. Predictors of mucormycosis in patients with cancer including concomitant sinusitis, voriconazole prophylaxis, the presence of multiple (> 10) nodules and pleural effusion at the time of CT have been proposed. Other clues such as chest wall cellulitis adjacent to the pulmonary lesion, reverse halo sign in chest radiography or CT, and presumed (by CT findings) fungal pneumonia with repetitively negative galactomannan levels may also prompt a high index of suspicion for mucormycosis. In our patient, mixed nodularity and halo sign at the left upper lobe led us to speculate invasive aspergillosis. However, a negative galactomannan test, inferior response to voriconazole, and the extent of dissemination suggested the diagnosis of mucormycosis. Although proven mucormycosis was diagnosed in our patient, the fungus culture was unable to yield any organism. In this setting, molecular techniques can help precisely identify the fungal species in a timely manner. Therefore, we suggest molecular diagnosis should be implemented with conventional histopathological examination if possible.
AmB, a polyene antifungal agent, was the cornerstone of mucormycosis therapy for decades. On the grounds of lower nephrotoxicity and the greater degree of safety at higher doses for a longer period of treatment, the lipid formulations of AmB are generally preferred. Posaconazole has demonstrated utility as salvage therapy for mucormycosis.\textsuperscript{14,15} Posaconazole may also be used as first-line therapy in patients with the presence or a reasonable expectation of renal dysfunction. In a retrospective case series, combination polyene plus caspofungin therapy was associated with significantly improved survival for patients with rhino-orbitocerebral mucormycosis compared with polyene monotherapy.\textsuperscript{16} Further study is warranted to determine whether polyene-echinocandin is indeed superior to polyene monotherapy.

In conclusion, we report a child with Ph\textsuperscript{+} ALL who developed disseminated \textit{Cunninghamella bertholletiae} infection during induction chemotherapy. We demonstrated the difficulties with invasive fungal infection in children with hematological malignancies. Our report highlights the necessity for physicians to keep high suspicion and awareness for this infrequent fungal infection in children with cancer.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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