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Successful Treatment of Disseminated Cryptococcal Infection in a Pediatric Acute Lymphoblastic Leukemia Patient During Induction

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Abstract

Disseminated cryptococcal infection is rarely reported in the setting of pediatric acute leukemia, despite the immunocompromised state of these patients. However, when present, disseminated cryptococcal infection poses treatment challenges and is associated with significant morbidity and mortality. Treatment of invasive fungal disease in a child with acute leukemia requires a delicate balance between anti-fungal and anti-neoplastic therapy. This balance is particularly important early in the course of leukemia, since both the underlying disease and overwhelming infection can be life threatening. We describe the successful management of life-threatening disseminated cryptococcosis in a child with acute lymphoblastic leukemia during induction therapy.

Keywords

cryptococcal; leukemia; pediatric; meningitis

INTRODUCTION

Cryptococcus neoformans is a fungal organism that is ubiquitous in the environment. There are two species of *Cryptococcus* that are considered pathogenic to humans: *Cryptococcus neoformans* and *Cryptococcus gattii*. *Cryptococcus neoformans* is the species most commonly found in the United States and other temperate climates. Acquisition of infection due to *Cryptococcus neoformans* occurs via inhalation of fungal elements, which are commonly found in bird droppings [1]. Common manifestations of cryptococcal infection include pneumonia, indolent meningoencephalitis, and fungemia. Disseminated cryptococcal infection involving the lungs and the central nervous system has been best characterized in HIV infected individuals and is associated with a high incidence of

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morbidity and mortality [2,3]. In the non-HIV infected pediatric population, disseminated cryptococcal disease is rare, with few case reports and small case series existing in the literature [4].

Despite the fact that patients with leukemia are immunosuppressed from both their underlying disease and treatment regimen, cryptococcal infection remains an unusual complication. In the setting of pediatric acute leukemia, disseminated cryptococcal illness is exceedingly rare and has previously been reported only twice in the literature in a patient early in the course of therapy [5,6]. We describe the successful treatment of a pediatric patient who developed disseminated cryptococcosis at the end of induction chemotherapy for acute lymphoblastic leukemia. Following anti-cryptococcal treatment and modification of his chemotherapeutic regimen, his leukemia remains in remission, and his infection remains quiescent 18 months from the onset of fungal disease.

CASE REPORT

A previously healthy nine-year-old boy was diagnosed with pre-B cell acute lymphoblastic leukemia (ALL). Although cytogenetics showed a deletion of chromosome 9p16, his leukemia was categorized as standard risk, and he was enrolled on the Children's Oncology Group study for standard risk ALL (AALL0331). He responded well to induction chemotherapy consisting of four weeks of daily oral dexamethasone, weekly intravenous vincristine, and a single dose of intramuscular PEG-asparaginase. A bone marrow evaluation on day 15 of induction demonstrated that his leukemia was in remission (with 2% blasts), and he completed Induction chemotherapy without apparent complications. He remained in remission on day 28 with no evidence of leukemic blasts in his bone marrow.

On day 30 of induction therapy the patient developed a fever. He was seen in the emergency department where he initially appeared well. A complete blood count (CBC) showed an absolute neutrophil count of 3,900/ μ L and an absolute lymphocyte count of 4,814/ μ L. Chest radiograph at that time was unremarkable. After blood cultures were drawn and a dose of intravenous ceftriaxone was administered, he was discharged home.

Less than 24 hours later, the patient returned to the emergency department with persistently high fever, headache, and moderate respiratory distress. A chest radiograph at that time revealed subtle bibasilar airspace opacities. He was treated with intravenous ceftazidime, intravenous azithromycin, and oral oseltamivir, and admitted to the inpatient unit for treatment of pneumonia. Over the subsequent 24 hours, his respiratory status worsened and he was transferred to the pediatric intensive care unit (PICU) for respiratory failure and septic shock. He was intubated, conventional mechanical ventilation was initiated, and he was started on vasoactive agents to support his blood pressure. The patient was initially started on empiric micafungin and fluconazole upon the first identification of yeast from the blood culture, and his port was replaced with a temporary central venous line at another site.

At the time of PICU admission, chest computed tomography revealed diffuse bilateral ground glass pulmonary opacities and mediastinal lymphadenopathy (Figure 1). A sepsis evaluation demonstrated the presence of cryptococcal antigen in his cerebrospinal fluid (titer 1:1). The blood cultures drawn at his initial presentation to the emergency department grew

Cryptococcus neoformans within eighteen hours, and a serum cryptococcal antigen was positive (titer 1024). At the time of speciation, liposomal amphotericin B was started at 5 mg/kg per day, and flucytosine was initiated at 100 mg/kg per day divided four times daily (standard starting doses). Daily blood cultures were positive for *Cryptococcus neoformans* for 5 subsequent days. Ocular examination and computed tomography scans of the brain, abdomen, and pelvis revealed no additional sites of fungal disease.

Over the next several days, the patient's septic shock and respiratory failure continued to worsen, necessitating escalation of support to include high frequency oscillatory ventilation, as well as additional vasoactive therapies for hemodynamic instability and septic shock. His dose of liposomal amphotericin B was increased to 7.5 mg/kg/day in response to this clinical deterioration. Because his ability to absorb enterically administered medication was questionable, oral flucytosine was stopped and intravenous fluconazole was initiated. A single loading dose of 25 mg/kg was given, followed by standard starting intravenous dosing of 12 mg/kg/day. The patient remained intubated and in critical condition for over two weeks. His clinical status gradually improved, and his blood cultures became negative five days after initiation of anti-fungal therapy. At this time, after one week of IV fluconazole, the patient's IV fluconazole was discontinued, and oral flucytosine was resumed. An increased dose was reinitiated based on low trough levels measured earlier in the hospital course. Flucytosine levels drawn when the patient was taking 100 mg/kg/day in 4 divided doses had revealed a trough of 7.1 mcg/mL (goal trough value is >25 mcg/mL), and a peak of 14.8 mcg/mL (goal peak value is <100 mcg/mL). The patient was therefore given flucytosine at 165 mg/kg/day in four divided doses upon restarting this medication. Subsequent testing revealed appropriate drug levels with a flucytosine trough of 73 mcg/mL.

Human immunodeficiency virus testing was negative, and lymphocyte enumeration 10 days into his illness revealed a CD4 count of 396 cells/mm³, consistent with moderate immunosuppression. In an attempt to prevent further immunosuppression in the setting of critical illness, chemotherapy was discontinued during this three-week period.

Approximately three weeks after the initial fever, following extubation, stabilization, and no further clinical manifestations of cryptococcal disease (including no neurological sequelae), chemotherapy was re-initiated with a "maintenance-like" regimen consisting of weekly methotrexate (20 mg/m²), and daily 6-mercaptopurine (75 mg/m²). This regimen of "maintenance-like" chemotherapy was continued for a total of three weeks, and six weeks after his initial presentation with fever, it was felt safe to resume standard Consolidation chemotherapy consisting of daily oral 6-mercaptopurine (75 mg/m²/day), a single dose of intravenous vincristine (2 mg/m²) and 3 doses of weekly intrathecal methotrexate (12 mg). As the patient was now clinically stable, he was started on consolidation dosing of fluconazole, 400 mg (~12 mg/kg) PO daily. His flucytosine and liposomal amphotericin B were simultaneously discontinued. The patient received Interim Maintenance and Delayed Intensification chemotherapy courses and started Maintenance therapy eight months after diagnosis, without further complications. Because of his continued chemotherapy induced immunosuppression, he will remain on this consolidation dosing of oral fluconazole until six months after his chemotherapy is completed.

The patient remains free of fungal disease, without neurologic deficits, and in clinical remission 18 months following this life-threatening episode of septic shock and respiratory failure due to infection with *Cryptococcus neoformans*.

This manuscript adheres to ethical standards and the Health Insurance Portability and Accountability Act (HIPAA), and informed consent was obtained for the clinical data included in this report.

DISCUSSION

Invasive fungal disease is a well-known complication in patients with acute leukemia, but cryptococcal infection is rare. The immune response against cryptococcal infection is primarily T-cell mediated, and the risk of cryptococcal infection is higher in patients with HIV and AIDS whose CD4 counts fall below 100 cells per microliter [2]. In patients with ALL, neutropenia is common, but CD4 counts often remain normal. However, CD4 cells in leukemia patients may be markedly functionally impaired due to corticosteroid administration commonly utilized in these patients. Despite this risk, there are very few case reports of cryptococcal fungemia or meningitis in non-HIV infected, non-transplanted children [5–10].

Disseminated cryptococcosis was previously a uniformly fatal diagnosis, but therapy for cryptococcal infection has dramatically improved over the past few decades as a result of advances in both antifungal and supportive therapies. However, outcome data for the immunocompromised, non-HIV-infected, non-transplanted pediatric population are lacking, because of the rarity of this occurrence.

The Infectious Diseases Society of America (IDSA) has published practice guidelines for the treatment of cryptococcal disease in a variety of settings, including the immunocompromised, non-transplant recipient, non-HIV infected child [11]. These guidelines include induction therapy with at least four weeks of intravenous amphotericin B deoxycholate at 1 mg/kg/day or intravenous liposomal amphotericin at 4–6 mg/kg/day with oral flucytosine at 100 mg/kg given as four divided doses. This induction is followed by consolidation therapy with high dose oral fluconazole for 8 weeks at 10 – 12 mg/kg/day, and then long term suppression therapy with lower dose oral fluconazole at 6 mg/kg/day.

Our patient received therapy in accordance with these guidelines, including 4 weeks of multi-agent induction therapy with liposomal amphotericin B with doses ranging between 5 – 7.5 mg/kg/day and flucytosine at doses ranging from 100 – 165 mg/kg/day, with dose adjustments based on serum flucytosine levels as described above. The patient subsequently received consolidation therapy with oral fluconazole dosing at 12 mg/kg/day. Because of his ongoing immunosuppression secondary to chemotherapy, it was decided to continue this consolidation dosing of fluconazole throughout the remainder of his chemotherapy, rather than decreasing to the 6 mg/kg/day IDSA suppression dosing regimen.

A critical issue raised by this case is how to balance the need for treatment of an overwhelming cryptococcal infection with therapy for underlying leukemia. In these circumstances, it is essential to not only cure the fungal infection, but also to maintain

leukemic remission. There are no specific guidelines and no published case reports that detail chemotherapeutic management options during disseminated fungal infection early in the course of chemotherapy for pediatric acute leukemia. However, the risks of further immunosuppression resulting from chemotherapy must be weighed against the risk of leukemia relapse in the absence of treatment. We chose to temporarily discontinue chemotherapy during the acute illness, so as not to compromise treatment of the fungal disease. This management strategy was not ideal for treatment of leukemia, but it was felt that this approach created the best chance for survival given that the leukemia was in remission at the time of infection. After clinical stabilization and initial treatment of cryptococcal disease, we then opted to use a “Maintenance-like” chemotherapeutic regimen in an effort to provide some anti-leukemic therapy without exacerbating the potential immunosuppression associated with Consolidation chemotherapy.

In summary, we describe the successful management of disseminated cryptococcal infection in an immunocompromised, non-HIV infected pediatric child in the induction phase of acute lymphoblastic leukemia. Reduced intensity chemotherapy during a period of systemic fungal illness, in combination with multi-agent anti-cryptococcal therapy, has resulted in resolution of fungal disease and continued leukemic remission 18 months later.

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Figure 1. Chest CT obtained 2 days after initial presentation of fungal illness demonstrates patchy bilateral ground glass opacities and bilateral pleural effusion.