Case Report

INVASIVE ESOPHAGEAL ASPERGILLOSIS ASSOCIATED WITH ACUTE MYELOGENOUS LEUKEMIA: Successful Therapy with Combination Caspofungin and Liposomal Amphotericin B

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Aspergillosis is one of the most common invasive fungal infections in patients with leukemia. In this patient group, this form of Aspergillus infection is a life-threatening condition with a mortality of 50–100%. The lungs are most often affected, but the esophagus can also be involved. The authors report the case of a child with leukemia who developed invasive esophageal aspergillosis. The condition was diagnosed by microscopic examination of endoscopic biopsy specimens. The patient was already receiving empirical liposomal amphotericin B when the diagnosis was made, so a second antifungal (caspofungin) was added to the regimen. This combination was successful. This case demonstrates a case of successful treatment of invasive esophageal aspergillosis using combination therapy of liposomal amphotericin B and caspofungin.

Keywords  acute myelogenous leukemia, Aspergillus, caspofungin, liposomal amphotericin B

Infection is the primary cause of morbidity and mortality in patients with hemato-oncologic malignancies. Current chemotherapy protocols have improved patient survival, but these intensive regimens often cause extended periods of profound neutropenia during which patients are susceptible to
opportunistic infections [1–3]. Candidiasis and aspergillosis are the most frequent invasive fungal infections among leukemia patients on chemotherapy.

Invasive aspergillosis is a life-threatening infection, and *Aspergillus fumigatus* accounts for approximately 90% of cases of this illness in patients with leukemia [1–3]. The reported mortality rates in this patient group range from 50 to 100% [1, 2]. The lung is the most common site of invasive *Aspergillus* infection. Other sites, such as the skin, eyes, brain, thyroid gland, paranasal sinuses, kidneys, bones, spleen, liver, and gastrointestinal system, are involved less frequently [3]. Primary esophageal aspergillosis is very rare during childhood.

Here we report the case of a young patient with acute myelogenous leukemia (AML) who developed invasive esophageal aspergillosis. The fungal infection was diagnosed by microscopic examination of endoscopic biopsy specimens of the esophagus.

**CASE REPORT**

A 15-year-old boy was admitted to our hospital with weakness, fever, and weight loss. Two years earlier, he had been diagnosed with French–American–British (FAB) AML-M7. The AML BFM 93 treatment protocol was prescribed, and the patient went into remission. However, he developed a fungal lung infection (fungus ball) during the initial phase of this chemotherapy protocol, as has been reported previously [4]. This was successfully treated with 2 weeks of liposomal amphotericin B (LAB) (5 mg/kg/day) followed by 4 weeks of itraconazole (400 mg/day). Clinical and radiological findings completely resolved at the end of this therapy. Thirteen months after he completed the AML BFM 93 protocol, the patient developed bone marrow relapse. He was hospitalized and treated with the IDA-FLAG regimen (idarubicin–fludarabine, cytarabine, and granulocyte colony-stimulating factor) followed by 2 courses of FLAG; however, he did not enter remission. The IDA-FLAG treatment caused severe neutropenia, pancytopenia, fever, and heartburn. The patient also developed severe pain in his back and epigastrium, accompanied by nausea, dysphagia, and frequent vomiting. He was unable to drink fluids.

Physical examination at this stage revealed abdominal distention due to massive splenomegaly, and epigastric tenderness on deep palpation. The patient was diagnosed with febrile neutropenia, and was treated with cefepime and amikacin. When there was minimal response to these agents, LAB was added as part of empirical treatment on day 7 (1 mg/kg/day). The patient’s back pain did not improve and he continued to exhibit dysphagia and vomiting, so a pediatric gastroenterology consultation was arranged.

During upper gastrointestinal endoscopy, we observed fragile, edematous, ulcerated, circumferential lesions covered with white plaques in the
Invasive Esophageal Aspergillosis Associated with Acute Myelogenous Leukemia

FIGURE 1 Upper gastrointestinal endoscopic images of invasive aspergillosis in a patient with AML. Note the severe circumferential ulceration with white plaques, and the severe narrowing of the esophagus.

lower third of the esophagus (Figure 1). The esophageal lumen was constricted to such a degree that the endoscope could not be passed into the stomach. Biopsies were collected from the involved region of the esophagus. The specimens were fixed in formalin and prepared with hematoxylin/eosin and metholamine silver stains because fungal infection was strongly suspected. Microscopic examination of the sections revealed fungal hyphae with characteristic 45-degree acute-angle branching (Figure 2). The patient was diagnosed with invasive esophageal aspergillosis.

Since he had already been given empirical doses of LAB (1 mg/kg/day) for the previous 18 days, histopathological examination showed invasive infection, and this was the second fungal infection during his cancer treatment, we decided to increase the LAB dose to 3 mg/kg/day and add a second antifungal drug to the regime. The patient was started on a 6-week course of caspofungin administered intravenously at 50 mg/day. Renal, hepatic, or other toxicity from the treatment regimen was not detected. Control upper gastrointestinal endoscopy and biopsy was performed 14 days after the LAB and caspofungin combination treatment was completed. This revealed significant mucosal healing but the severe esophageal stenosis remained. The patient underwent gastrostomy and subsequent esophageal balloon dilatation. After 9 sessions of balloon dilatation, he was able to swallow fluids and
eventually solids. However, he died because of multiorgan failure secondary to leukemic infiltration 8 months after the relapse of AML.

**DISCUSSION**

*Aspergillus* infection most often affects the lungs, but can often involve the sinonasal passages and the upper respiratory tract. These fungi can occasionally invade deeper tissues and disseminate via the bloodstream to become a life-threatening infection. This is a particular risk in immunocompromised children. *Aspergillus* fungemia must be considered in any immunosuppressed leukemia patient who develops antibiotic-resistant fever while a central venous catheter is in place. The main risk groups are children with acquired immunodeficiency syndrome or leukemia, and patients on immunosuppressive therapy [1–3]. Although T-cell function and macrophage activation are intact in patients with acute leukemia, these individuals often experience extended periods of profound neutropenia due to intensive chemotherapy, and this can lead to opportunistic infections.

Leukemia patients are at risk for infection with *Aspergillus* or *Candida* species both in the community and as nosocomial infections. *Aspergillus*...
species are known to occasionally cause esophagitis, as are other invasive fungal organisms such as *Mucor*, *Histoplasma*, and *Cryptococcus* species. These microorganisms can be diagnosed by examining sputum, bronchial washes, fine-needle aspirates, and esophageal brushings [5, 6]. *Aspergillus* esophagitis can be diagnosed based on histopathological examination of esophageal tissue specimens obtained during upper gastrointestinal endoscopy. One report states that cytological/microbiological examination of esophageal brushings is a sensitive diagnostic test as well [6]. In cases of *Candida* or *Aspergillus* infection of the esophagus and esophageal malignancy, brushing can complement endoscopic biopsy in establishing the diagnosis. Tissue specimens from esophageal aspergillosis show fungal hyphae with characteristic 45-degree acute-angle branching, as we observed in our case [5, 6]. It is concluded that direct microscopic examination of a clinical specimen is a crucial first-line procedure in detecting the presence of fungal elements and is perhaps the most rapid, useful, and cost-effective means of diagnosing fungal infections [7]. However, immunohistologic staining for the exact identification of fungi in clinical specimens has been attempted and monoclonal and polyclonal fluorescent-antibody reagents have been developed for the differentiating the genera of *Aspergillus*, *Fusarium*, and *Scedosporium* in situ. In our study, we could not perform immunohistologic staining and culture of the material failed to give a definitive result. However, we diagnosed the patient with aspergillosis with endoscopic and histopathological findings. Isolation of *Aspergillus* spp. from esophageal brushings or biopsy specimens may indicate a grave prognosis [5]. For children with AML who develop invasive aspergillosis, survival depends on early diagnosis and aggressive therapy, together with improvement in hematologic status [5, 6].

Until recently, conventional amphotericin B deoxycholate was considered the drug of choice for primary treatment of aspergillosis, but it was ineffective in approximately 50% of patients with invasive aspergillosis [8, 9]. LAB is better tolerated than amphotericin B deoxycholate [8] and is less toxic at doses between 7.5 and 15 mg/kg/day [10]. A significant proportion of patients with invasive *Aspergillus* infection do not respond to treatment with conventional or lipid-formulation amphotericin B [8, 9].

Caspofungin is the first echinocandin that has been shown to inhibit the synthesis of 1,3 β-D-glucan by *Aspergillus* species [8, 9, 11]. It appears that most patients with invasive aspergillosis require combined treatment, such as caspofungin and LAB, for at least 3 weeks. Research has shown this regimen to be effective in 75% of patients with leukemia [12, 13]. Multiple studies have demonstrated that caspofungin has additive or synergistic effects when used with amphotericin B or voriconazole [12]. We administered a 6-week course of caspofungin combined with LAB, and this was successful in our case. During the first treatment attempt with BFM protocol, the patient had been successfully treated for a fungal lung infection (fungal ball) using LAB followed by itraconazole.
In conclusion, clinicians managing patients with acute leukemia who are neutropenic should keep a high index of suspicion for infections such as invasive aspergillosis, and must administer treatment promptly. This report emphasizes the importance of gastrointestinal endoscopic examination of immunocompromised patients with vague gastrointestinal complaints. Combined antifungal treatment modalities could be useful in cases with invasive esophageal aspergillosis.

REFERENCES


