Zygomycosis in a Child with Severe Aplastic Anemia Who has Invasive Pulmonary Aspergillosis: Hypersensitivity Reaction to Liposomal Amphotericin B and Successful Challenge

İnvaziv Pulmoner Aspergillozis Enfeksiyonu Sırasında Zigomikoz Gelişen Ağır Aplastik Anemili Olguda Lipozomal Amfoterisin B Allerjisi ve Desensitizasyon

Yılmaz Ay[1], Deniz Yılmaz[1], Can Balkan[1], Bülent Karapınar[2], Levent Midyat[3], Mehmet Akın[1], Kaan Kavaklı[1]

[1]Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Hematoloji Bilim Dalı, *Bornova, Turkey*

[2]Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Yoğun Bakım Ünitesi, *Bornova, Turkey*

[3]Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Solunum Allerji Bilim Dalı, *Bornova, Turkey*

Abstract

Invasive pulmonary aspergillosis and zygomycosis are fungal opportunistic diseases with a high morbidity and mortality rate, predominantly affecting immunosuppressed patients. In patients with severe aplastic anemia (SAA) more than one invasive mycotic infection should be considered and early diagnosis with adequate treatment is crucial. We present a patient with treatment resistant SAA who developed zygomycosis while under caspofungin + voriconazole combined antifungal therapy for invasive pulmonary aspergillosis. A 13.5 year old boy with SAA developed invasive pulmonary aspergillosis. Liposomal amphotericin B (L-AmB) was started, but he developed an anaphylactic type hypersensitivity reaction with L-AmB. Therefore treatment was changed to voriconazole treatment, and at the 3rd month of this treatment, caspofungin was added as a salvage therapy. However, he did no respond to immunosuppressive treatment for SAA. No clinical or laboratory improvement of invasive fungal infection was seen in spite of antifungal therapy. Clinical nasal/paranasal zygomycosis occurred and showed a very rapid spread to most parts of the face under this intensive antifungal therapy. Although no destruction of the bones was seen on tomography at first, a fungal infection was suspected and histopathologic / micologic cultures proved the diagnosis. L-AmB was given with a protocol allowing desensitization since the patient had a history of anaphylactic reaction. This case report is presented in order to illustrate the possibility of more than one fungal infection in an immuncompromised patient in spite of antifungal therapy and documenty a successful L-AmB challenge and possible desensitization in a patient with

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Correspondence Address:
Yazışma Adresi:
Dr. Yılmaz Ay
Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Hematoloji Bilim Dalı,
Bornova, Turkey
Phone: +90 232 390 10 01
E-mail:
dryilmazay@yahoo.com

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Özet

İnvaziv pulmoner aspergillozis ve zigomikozlar, özellikle bağışıklık sistemi baskılanmış hastalarda morbidite ve mortaliteye neden olan fırsatçı mantar enfeksiyonlarıdır. Ağır aplastik anemili (AAA) hastalarda birden fazla invaziv fungal enfeksiyon olabileceğinin akılda tutulması, erken tanı ve uygun tedavi çok önemlidir. Tedaviye dirençli çok AAA'li hastada, invaziv pulmoner aspergillozise yönelik vorikonazol + kaspofungin kombine antifungal tedavisi verilirken gelişen zigomikoz enfeksiyonu sunuldu. AAA'li 13.5 yaşındaki erkek olguda invaziv pulmoner aspergillozis enfeksiyonu saptandı. Lipozomal amfoterisin B (L-AmB) başlandı. Ancak, hastada L-AmB tedavisi sırasında anaflaktik reaksiyon gelişti. Bu yüzden, antifungal tedavi vorikonazol olarak düzenlendi. Vorikonazol tedavisinin 3. ayında, kurtarma tedavisi amacıyla kaspofungin eklendi. AAA'li olguda immunsupresif tedaviye olumlu yanıt alınamadı. İkili antifungal tedaviye rağmen invaziv pulmoner aspergillozis enfeksiyonunda klinik ve laboratuar olarak iyileşme saptanmadı. İzleminde klinik olarak nasal/paranazal zigomikoz enfeksiyonundan kuşkulanıldı. Yoğun antifungal tedaviye rağmen enfeksiyon hızla maksiller bölgeye yayıldı. Enfeksiyon ilk başladığında çekilen tomografide kemik yapılarda destrüksiyon görülmemesine karşın histopatolojik ve mikolojik olarak zigomikoz teşhisi konuldu. L-AmB ile anaflaktik reaksiyon öyküsü nedeniyle L-AmB tedavisi, desensitizasyon ile birlikte başarılı bir şekilde verildi.

İmmunsupresif hastalarda antifungal tedavi altında dahi birden fazla invaziv fungal enfeksiyon gelişebileceği, ayrıca L-AmB'ye alerjisi olan hastalarda başka tedavi alternatifi yoksa desensitizasyon ile

SAA who had a prior anaphylactic reaction associated with L-AmB. *(J Pediatr Inf 2011; 5: 22-5)*

Key words: Invasive pulmonary aspergillosis, zygomycosis, hypersensitivity reaction to Liposomal Amphotericin B, aplastic anemia

L-AmB verilebileceğini vurgulamak amacıyla bu hasta sunulmuştur. *(J Pediatr Inf 2011; 5: 22-5)*

Anahtar kelimeler: İnvaziv pulmoner aspergilloz, zigomikoz, liposomal amfoterisin B alerjisi, aplastik anemi

Introduction

Acquired aplastic anemia (AAA) may be idiopathic or secondary. About 70% of cases are considered idiopathic, without any identifiable cause. In severe aplastic anemia allogeneic bone marrow transplantation is the recommended therapy when an HLA-matched sibling donor is available. In the absence of an HLA-matched sibling marrow donor the patients should be treated with ATG, cyclosporine A, methylprednisolone and growth factors such as G-CSF. If there is no response to the immunosuppressive therapy, HLA-matched unrelated bone marrow transplant should be considered when a suitable donor is available. High-dose cyclophosphamide and cyclosporine therapy without stem cell transplant is carried out in some institutions (1).

In these patients neutropenia, caused by the disease itself or immunosuppressive therapy, leads to serious infections and the patient's survival mostly depends on the management of infections. It is suggested that severe aplastic anemia patients with fever and neutropenia should be treated with broad-spectrum antibiotic coverage. In patients who remain febrile 4-7 days in spite of broad antibacterial coverage, antifungal therapy with amphotericin B should be started empirically. Liposomal amphotericin B (L-AmB) has a wide antifungal spectrum including most kinds of *Candida, Aspergillus spp*. and Zygomycosis.

Sensitization and anaphylactic reaction to L-AmB is a rare problem among children with aplastic anemia and can be mostly solved by changing antifungal treatment to other drugs such as caspofungin and voriconazole. However, in the presence of infection with zygomycosis, there is no alternative intravenous treatment option. In this situation, desensitization which is used rarely should be considered.

This case report documents a successful L-AmB challenge and possible desensitization in a very severe neutropenic patient with AAA who had aspergillosis as well as zygomycosis and had a prior anaphylactic reaction associated with L-AmB.

Case

A 13.5 year old boy was admitted to our hospital with pancytopenia. We learned from the history that he had contracted hepatitis A two months previously. Physical examination showed no hepatosplenomegaly. Laboratory findings revealed pancytopenia with agranulocytosis (WBC: 690 /mm^3, HB: 7.5 g/dl, HCT: 22%, MCV: 85 fl, PLT: 5000/mm^3, reticulocyte: 0.4%) Bone marrow biopsy showed decreased cellularity (below 5%). Diepoxybutane test was negative. No cytogenetic abnormality was detected.

He was diagnosed as very severe aplastic anemia secondary to Hepatitis A. There was no available HLA matched sibling donor. He received anti thymocyte globulin (ATG- Fresenius«, dose: 2.5 mg/kg/day for 8 days), cyclosporine (5-10 mg/kg/day for 180 days), prednisolone (2 mg/kg/day for 8 days, then dose tapered and stopped at the 28th day) and Granulocyte colony stimulating factor (G-CSF) was started at the 5th day of ATG at the dose of 5 mcg/kg/day for 40 days. His blood count did not show any change and after 6 months, he received the second course of ATG at the same dosages. His bone marrow biopsy and blood count did not recover. Severe neutropenia persisted.

Patient developed febrile neutropenia 3 weeks after the 2nd course of ATG treatment. At the 6th day of febrile neutropenia, empiric L-AmB was started at the dose of 3 mg/kg/day without evidence of fungal infection (Thorax tomography was normal, galactomannan test was negative, blood cultures were negative). At the 4th day of L-AmB treatment he had an anaphylactic reaction against L-AmB and treatment was changed to voriconazole. Two weeks after initiation of voriconazole treatment he developed tacyhpnea and cough. High fever persisted. Chest X Ray showed pulmonary infiltration in the superior lobe of the right lung (Figure 1). Thorax tomography revealed pulmonary focal consolidation areas in the superior and inferior lobes of the right lung with abscess formation (Figure 2). Galactomannan test was found to be positive three times. He underwent hemithoracotomy at the 5th week of voriconazole treatment. Although normal platelet count and bleeding diathesis was corrected by adequate replacement therapy preoperatively, severe bleeding from the operation site was seen during surgery. Therefore lobectomy could not be performed and a biopsy was taken from the lesion. Histopathological assessment of the tissue showed hyphaes consistent with *Aspergillus spp.* and *Aspergillus spp.* was identified from tissue cultures. No infectious agent was detected in the specimen of bronchoalveolar lavage and caspofungin was added to

voriconazole as salvage therapy at the 6th week of voriconazole treatment (2). He showed a stable condition without any improvement or progression of pulmonary symptoms, fever, neutropenia and thorax tomography findings.

He was given high dose cyclophosphamide (50 mg/kg/day for 4 days) and G-CSF (5 mcg/kg/day) 14 weeks after the last ATG treatment. However, no laboratory or clinical recovery of aplastic anemia was seen. Fever and severe neutropenia persisted despite combination therapy with voriconazole and caspofungin for 12 weeks.

He developed edema, hyperemia in the right orbit, and ecchymoses in the right superior palpebra. Immediate evaluation with paranasal/orbital tomography showed mucosal thickening of bilateral ethmoid sinuses with loss of aeration. No destruction was found. Within a few hours necrosis appeared in the hard palate and nasal area (Figure 3) and showed rapid spread. Cutaneous biopsy was taken from the nasal area and its histopathological assessment demonstrated hypae morphology consistent with mucormycosis. Mucormycosis was identified from culture from biopsy samples. Because the patient had a history of anaphylactic reaction to L-AmB, desensitization was considered. At the same day that clinical findings were seen, challenge with L-AmB was performed in the intensive care unit as outlined in Table 1, as defined previously (3). He tolerated the challenge procedure, and his vital signs were within normal ranges during 6 hours. He continued to tolerate L-AmB, in daily doses of up to 5 mg/kg. Voriconazole was stopped and Caspofungin treatment was continued. Six days after the diagnosis of paranasal mucormycosis and initiation of L-AmB treatment the patient expired.

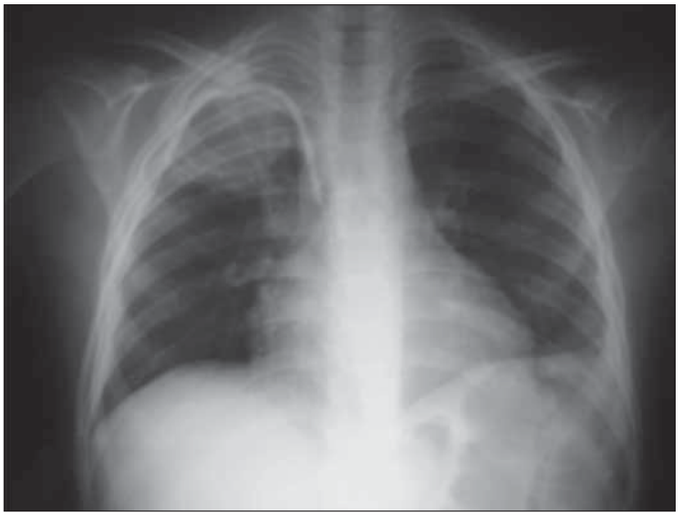

Figure 1. Chest X Ray showed pulmonary infiltration in the superior lobe of right lung

Table 1. Amphotericin B challenge and desensitization protocol

1.	Procedure supervised by physician
2.	Epinephrine 1: 1000 wt/vol, multidose vial at bedside
3.	Ventilation parameters, invasive arterial monitorization and ECG were followed during the desensitization
4.	Premedication with methylprednisolone, 60 mg, IV and dipenhydramine, 25 mg, IV
5.	Amphotericin B (ambisome)* administration Schedule
	a. 10^{-6} dilution, infused over 10 min
	b. 10^{-5} dilution, infused over 10 min
	c. 10^{-4} dilution, infused over 10 min
	d. 10^{-3} dilution, infused over 10 min
	e. 10^{-2} dilution, infused over 10 min
	f. 10^{-1} dilution (1.0 mg), infused over 30 min
	g. 30 mg in 250 ml 5% dextrose, infused over 4 hr

IV, Intravenously
*Mixtures were prepared in 10 ml 5% dextrose by the hospital intensive care unit pharmacy, unless otherwise noted

Discussion

SAA can be seen as an uncommon complication after acute hepatitis A infection (4,5). In SAA patients, infections are inevitable, especially during and after treatment with very potent immunosuppressive agents. Prolonged neutropenia may cause invasive fungal disease. *Aspergillus* and *Candida spp*. are the most common causes of invasive fungal infections in these patients. For primary treatment of invasive pulmonary aspergillosis, i.v. or oral voriconazole is recommended for most patients (A-I), and for seriously ill patients, the parenteral formulation is suggested (A-III) (6). Combination of caspofungin and an azole or an amphotericin B formulation can be used as salvage therapy in invasive fungal infections (2).

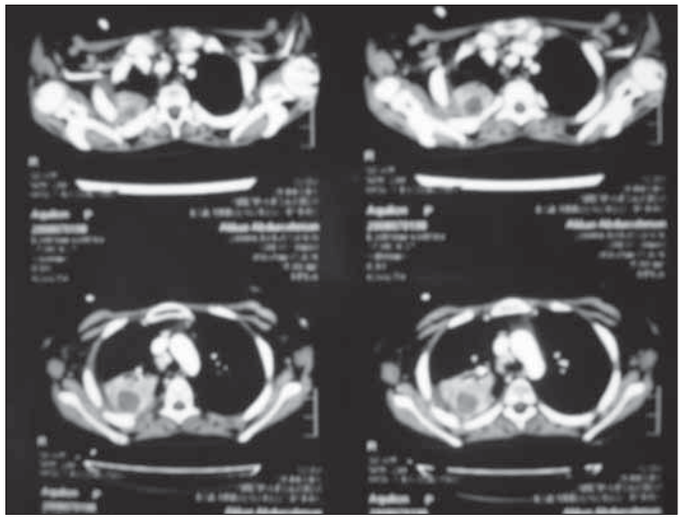

Figure 2. Thorax tomography revealed pulmonary focal consolidation areas in superior and inferior lobes of the right lung with abscess formation

Figure 3. Necrosis appeared on nasal area and showed rapid spread

Invasive zygomycosis is a very rare fungal opportunistic disease with a high morbidity and mortality rate predominantly affecting immunosuppressed patients such as leukemias, congenital or acquired aplastic anemias. The increase in zygomycosis was coincident with an incremented use of voriconazole and caspofungin (7-9) and with an increased number of immunosuppressed patients (7). Intravenous administration of L-AmB is the treatment of choice for disseminated fungal infections, but numerous acute and long-term side effects limit its use. Anaphylaxis associated with L-AmB is quite rare and here we describe an L-AmB challenge or desensitization in a patient with L-AmB induced anaphylaxis. Zygomycosis in patients with persistent neutropenia is found to be associated with poor outcomes despite aggressive surgical and antifungal therapy (10). Surgical treatment together with systemic, high doses of L-AmB, posaconazole, and caspofungin cured the local infection and controlled systemic lesions (11).

In the present patient no response was seen with ATG treatment and there was no available donor for hematopoietic stem cell transplantation. The patient developed pulmonary aspergillosis and combination therapy with caspofungin and voriconazole did not improve the clinical and laboratory status. Under this combined antifungal therapy zygomycosis occurred. Since the patient had an anaphylactic type hypersensitivity reaction to L-AmB before, it was given with desensitization. L-AmB dose was increased to 5 mg/kg/day and no allergic reaction was seen.

The rare invasive mycotic infections should be kept in mind even though the patients are under antifungal therapy. Destruction is not always present, especially in the early phase of the disease. If there is a strong clinical suspicion of zygomycosis, prompt tissue biopsy should be obtained. Histopathologic assessment and cultures for bacterial and mycologic agents should be performed urgently. Efficacy of antifungal treatment with L-AmB depends on early recognition and aggressive intervention. Early diagnosis and adequate therapy can lower mortality. Rapid progression and unstable vital functions in our patient did not allow debridement of the tissue. Patient expired due to persistent invasive pulmonary aspergillosis and zygomycosis which appeared during the intensive antifungal therapy.

In conclusion, rare invasive fungal infections should be always considered in patients with very severe aplastic anemia. More than one invasive fungal infection can be seen in these patients (12). Early treatment with adequate antifungal agents and, if possible, debridement are crucial. L-AmB challenge is safe and well tolerated, as demonstrated in this case report. Avoidance of opiates, which perturb mast cells, and premedication with corticosteroids and antihistamines are recommended.

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