

Treatment of Invasive Pulmonary Aspergillosis by Combined Intravenous and Transthoracic Injection of Amphotericin B in a Patient with Acute Leukemia : A Case Report¹

Choong Ki Park, M.D., Dong Woo Park, M.D., Yong Soo Kim, M.D., Yo Won Choi, M.D.,
Seok Chol Jeon, M.D., Heung Suk Seo, M.D., Chang Kok Hahm, M.D., Myung Ju Ahn, M.D.².

Invasive pulmonary aspergillosis may be a major cause of lethal opportunistic infection in neutropenic patients. The purpose of this report is to describe a combined treatment modality involving transthoracic injection of amphotericin B and gelatin solution for persistent mycetoma within the cavity. Mycetoma may interfere with consolidation chemotherapy after intravenous injection of amphotericin B for invasive pulmonary aspergillosis in a patient with acute monocytic leukemia in whom neutropenia developed during remission induction chemotherapy.

Index words : Aspergillosis
Lung, infection
Interventional procedures

Case Report

A 56-year old man was admitted to the hospital via emergency room complaining of shortness of breath and generalized weakness. Two weeks earlier he had developed symptoms of fever, chill and exertional dyspnea. He had a ten-year history of hypertension which had been intermittently treated with antihypertensive drugs. His body temperature was 38°C, pulse rate was 120/min., and respiration rate was 28/min. Blood pressure was 70/50 mmHg.

On physical examination the patient looked acutely ill and left periorbital swelling, tenderness and pus discharge suggesting periorbital cellulitis were noted. On auscultation fine inspiratory wheezing and crackling sounds were noted at the base of the right lung. The liver was palpable 4 cm below the right costal margin and the spleen 5 cm below the left costal margin. Initial CBC was as follows: WBC 50,350/mm³, Hb 12.9 g/dl, Hct 37%, platelet 154,000/mm³. Blasts >80% were noted on peripheral blood smear. In bone marrow

aspirates normal hematopoietic cells were totally replaced by leukemic cells. The blast cells were strongly positive to non-specific esterase, but negative to Sudan Black B or Periodic-acid Schiff (PAS) stain. The immunophenotype confirmed myeloid differentiation of the malignant clones: CD 13+, CD 33+, CD 45+ and HLA-DR+. Acute monocytic leukemia (M5a) was diagnosed. A chest radiograph showed pneumonic consolidation in the right lower lobe.

To control this life-threatening infection, empirical treatment with broad spectrum antibiotics containing ceftazidime (Fortum®, Korea Glaxo, Korea), aminoglycoside (Amikacin®, Boryung, Korea), and vancomycin was started. Methicillin-resistant *Staphylococcus aureus* was found in culture of both sputum and eye discharge. On the sixteenth hospital day, the patient was recovering and pneumonic consolidation and periorbital cellulitis had both improved. On the seventeenth hospital day, the patient underwent induction chemotherapy, with continuous intravenous infusion of cytosine arabinoside 200 mg/m² for 7 days and idarubicin 12 mg/m² for 3 days. A prophylactic antifungal agent, fluconazole 200 mg/day, was also given for 14 days. During the remission induction period, the patient was relatively well until severe myelo-suppression developed. The duration of absolute neutrophil count less than 500/mm³ was 18 days;

¹Department of Diagnostic Radiology, Hanyang University, College of Medicine

²Department of Internal Medicine, Hanyang University, College of Medicine

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Address reprint requests to: Choong Ki Park, M.D., Department of Diagnostic Radiology, Hanyang University Kuri Hospital, # 249-1, Kyomoon-dong, Kuri-si, Kyoungki-do, Korea, 471-701

Tel. 82-346-560-2542 Fax. 82-346-560-2551

the lowest count was $110/\text{mm}^3$.

On the fourteenth day of the neutropenic period, another episode of high fever began with productive cough and a large amount of sputum. A chest radiograph showed pneumonic consolidation in the left upper lobe with an air crescent sign, thus suggesting invasive pulmonary aspergillosis (Fig. 1A). Because of the prolonged neutropenia, empirical treatment with an antifungal agent, amphotericin B, was considered. To confirm invasive pulmonary aspergillosis, fine needle aspiration was performed. On the H & E stain of the aspirates, typical branching aspergillus hyphae were noted (Fig. 1B). After intravenous administration of the therapeutic dose (1mg/kg/day) of amphotericin B, consolidation of the left upper lobe rapidly resolved. At that time, the neutrophil count returned to its nor-

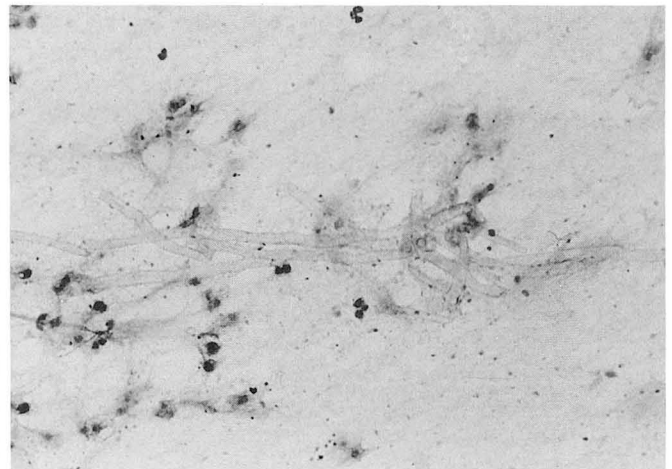
mal level. On the thirtieth day of remission-induction chemotherapy, bone marrow aspirates showed that remission was complete.

Serial follow-up showed considerable resolution of left upper lobe consolidation, but a cavitory lesion still remained, even after four weeks' treatment with amphotericin B. We therefore decided to locally inject amphotericin B into the cavity, prior to further chemotherapy.

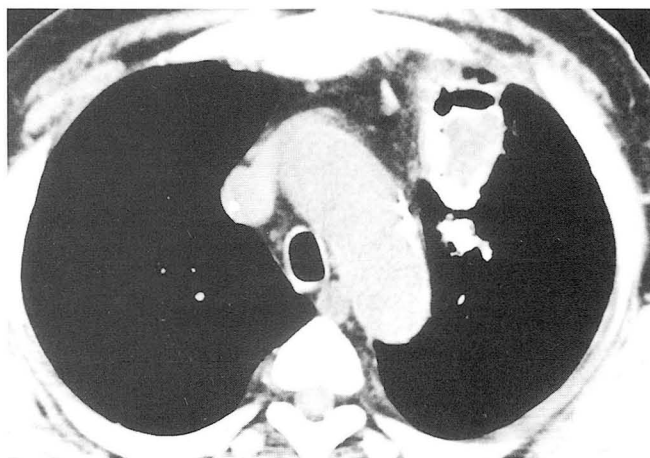
Amphotericin B gelatin solution consisted of 12 g of gelatin (Unipath, Basingstoke, Hampshire, England) dissolved in 10 ml of sterile water, 50 mg of amphotericin B, and 1 ml of lipiodol. The tip of an 18 gauge spinal needle was introduced into the cavity, and 10 ml of the mixture heated in a 40°C water bath was injected without complications. The interior and peripheral



A



B



C



D

Fig. 1. A. Initial high-resolution CT scan at the level of aortic arch shows air-crescent sign within the consolidation of left upper lobe with central homogeneous mass, suggesting invasive aspergillosis.

B. Photomicrograph shows typical branching pattern of aspergillus hyphae (H & E stain, $\times 400$)

C. Four weeks' follow-up CT scan near the same level as (A) shows intracavitary injected amphotericin-gelatin solution within the persistent cavity.

D. Two months' follow-up CT scan near the same level as (C) shows a thin-walled cavity without containing aspergilloma.

areas of the cavity were opacified by radiopaque lipiodol-amphotericin B gelatin solution (Fig. 1C). Serial radiography was performed weekly and follow-up CT scanning two months later. The radiographs showed that the cavity had almost disappeared; according to CT images only a small thin-walled cavity remained (Fig. 1D). After two sessions of consolidation chemotherapy, the leukemia had improved and the cavity had healed; it was seen on follow-up radiography as an opaque line.

Discussion

Pulmonary aspergillosis is classified as either saprophytic aspergilloma, allergic bronchopulmonary aspergillosis, or invasive or semi-invasive aspergillosis(1); four forms are not mutually exclusive. Invasive aspergillosis occurs primarily in profoundly immunocompromised patients. Although hyphae can be found along the surface and within the fibrous wall of the cavity, invasion of adjacent lung parenchyma does not occur unless host defense mechanisms are compromised(2). With the increasing use of aggressive chemotherapy in patients with malignancy causing prolonged leukopenia, the risk of invasive aspergillosis has increased.

The predominant pathologic abnormalities of invasive aspergillosis are tissue invasion, abscess formation, and angioinvasion with or without infarction(3). In its semi-invasive form the fungus may produce extensive local consolidation and destruction of lung parenchyma. There need not be a previous cavity. Pulmonary consolidation involves progressive cavitation and subsequent mycetoma formation. In our case, meniscus shaped air density developed within the consolidation during the neutropenic state. After intravenous injection of amphotericin B, the outer portion of the consolidation was resolved.

In invasive aspergillosis, the prognosis is poor; pulmonary disease progresses, and in many patients dissemination leads to death. Lives can be saved only by early diagnosis and treatment. For this reason there seems to be general agreement that when the diagnosis is suspected, empirical treatment with fungicides

should be promptly initiated (4). Young(5) reported that eight neutropenic patients with invasive aspergillosis who underwent emergency lung resection suffered no major complication. Surgery is hazardous, however, mortality and morbidity increase. During systemic treatment involving intravenous administration of antifungal agents, there is substantial risk of nephrotoxicity and hepatotoxicity(6). Lee (7) reported that percutaneous intracavitary instillation of amphotericin B is a safe and effective method of treating hemoptysis caused by aspergilloma. Munk (8) reported the use of amphotericin B gelatin injection for the control of hemoptysis in three inoperable patients with mycetoma. In a patient with invasive pulmonary aspergillosis, direct injection of an antifungal drug (amphotericin B gelatin solution) may control the condition and allow continuous chemotherapy.

In conclusion, we have described a case with invasive aspergillosis in a patient with leukemia who was successfully treated by combined therapy involving intracavitary injection of amphotericin B and gelatin solution after intravenous injection of amphotericin B.

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급성 백혈병 환자에서 암포테리신 B의 경정맥 및 경흉부 혼합주입에 의한 침습성 폐아스페르길루스증의 치료: 1예 보고¹

¹한양대학교 의과대학 방사선과학교실

²한양대학교 의과대학 내과학교실

박충기 · 박동우 · 김용수 · 최요원 · 전석철 · 서홍석 · 함창곡 · 안명주²

침습성 폐아스페르길루스증은 호중구감소증 환자 사망의 주 원인이다. 저자들은 급성 단핵구성 백혈병 환자에서 항암제 투여 중에 발생한 호중구감소증과 합병된 침습성 폐아스페르길루스증을 암포테리신 B의 경정맥 주입으로 치료하여 호전되었지만 공동내 균종이 남아 있어 암포테리신 B와 젤라틴 혼합물을 공동 내로 주입하여 성공적으로 치료된 증례를 보고하고자 한다.