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CASE REPORT

**Kazunori Nakase · Akira Yazaki · Sigehisa Tamaki
Motoaki Tanigawa · Kota Tsuji · Eiki Miyanishi
Hiroshi Shiku**

Effect of direct infusion of antifungal agent on invasive pulmonary aspergillosis in a patient with acute leukemia

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Abstract Invasive pulmonary aspergillosis is a serious problem in the treatment of patients with acute leukemia. A 52-year-old woman with acute myeloid leukemia developed invasive pulmonary aspergillosis during remission induction chemotherapy. Initially, we treated her with a continuous intravenous drip infusion of amphotericin B, together with itraconazole, given orally. A peripheral crescentic cavity formed in the fungal lesion after the number of neutrophils recovered, and we therefore performed a direct infusion of miconazole into the cavity transbronchially. The lung lesion resolved dramatically shortly after this treatment. In this patient, the transbronchial infusion of an antifungal agent seemed to have been very useful for bringing about prompt resolution of the fungal lesion.

Key words Invasive pulmonary aspergillosis · Acute leukemia · Transbronchial infusion

Introduction

Invasive pulmonary aspergillosis (IPA) is a major and often a fatal infectious complication in patients with acute leukemia receiving intensive chemotherapy.[1,2] If this fungal disease occurs, chemotherapy for acute leukemia must be discontinued until the disease resolves, and this would increase the risk of regrowth of leukemic cells. Accordingly, treatment of this disease that leads to rapid resolution is a very important issue.

In the present report, we describe a patient with acute myeloid leukemia who developed IPA during remission induction chemotherapy. In addition to an intravenous drip infusion of amphotericin B (AmB) together with itraconazole given orally, direct injection of miconazole into a cavity that formed in the peripheral fungal lesion led to dramatic resolution of the IPA. This case indicated the usefulness of the intracavitary administration of an antifungal drug in order to shorten the duration of treatment for IPA.

K. Nakase (✉) · A. Yazaki · H. Shiku
The Second Department of Internal Medicine, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
Tel. +81-592-32-1111; Fax +81-592-31-5200
e-mail: k-nakase@amigo.ne.jp

S. Tamaki · M. Tanigawa · K. Tsuji · E. Miyanishi
Department of Internal Medicine, Yamada Red Cross Hospital, Watarai-gun, Mie, Japan

Case report

A 52-year-old woman (body weight, 46.1 kg) had felt general fatigue since July 1997, and developed cough and a high fever on August 25. Pancytopenia was noted by a physician, and she was referred to Yamada Red Cross Hospital for further evaluation, on September 11. Hematological data revealed: white blood cell count of 1500/μl with 40% blast cells, platelet count of 4.1×10^4/μl, and red blood cell count of 103×10^4/μl. Bone marrow aspiration showed a nuclear cell count of 23.6×10^4/μl with 90.4% blast cells. The blast cells were positive for myeloperoxidase, CD13, CD33, CD34, and HLA-DR. She was diagnosed with acute myeloid leukemia (M1 French-American-British [FAB] criteria). Chest X-ray disclosed a slight patchy shadow in the upper region of the right lung. She was treated with antibiotics; cefozopran (1 g twice a day, drip infusion) and amikacin (100 mg twice a day, drip infusion) for suspected bacterial pneumonia. Induction chemotherapy (idarubicin and cytarabin) for acute myeloid leukemia was started simultaneously. As antifungal prophylaxis, fluconazole (200 mg once a day, orally), AmB inhalation, with a nebulizer (four times a day; total dose of 50 mg per day), and AmB in sterile water, as a gargle (four times a day), were administered.

Ten days after the initiation of the induction chemotherapy, her neutrophil count had decreased to less than 500/mm^3 and she manifested hemosputum. She was isolated in a room (with a clean bed) equipped with a high-efficiency particulate air filtration (HEPA) system during the period when the neutrophil count was less than 500/mm^3. Her

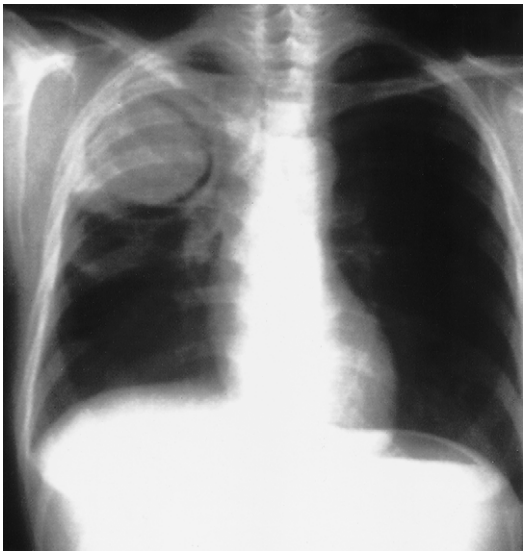

Fig. 1. Chest X-ray shows an aspergillus lesion in the upper region of the right lung. A crescentic cavity was found surrounding the core lesion

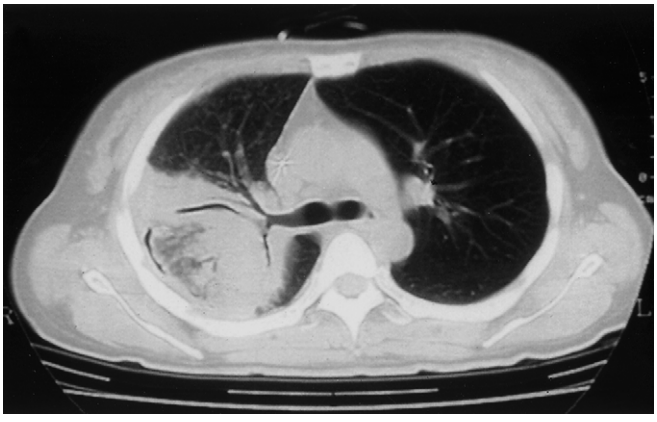

Fig. 2. Computed tomography scan shows a branch of the right bronchus connecting with the crescentic cavity surrounding the core lesion

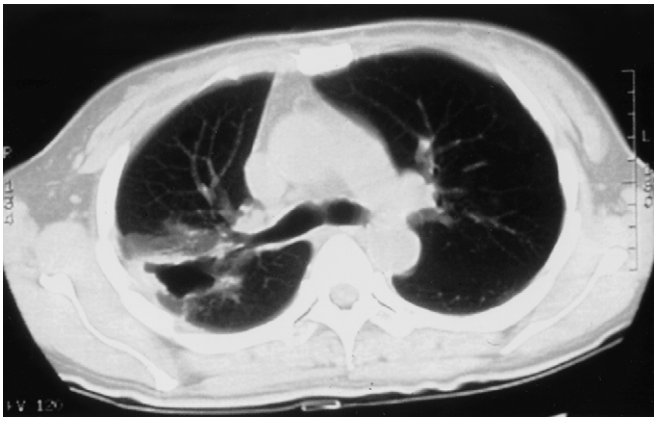

Fig. 3. Computed tomography scan shows shrinkage of the fungal lesion

serum level of β-D-glucan was elevated (46.4 pg/ml), and therefore the oral fluconazole was replaced by AmB (initially, 1 mg/day and increased to 50 mg/day in 5 days; continuous drip infusion for 24 h) together with itraconazole (200 mg/day, orally). After recovery of the number of neutrophils to more than 1000/mm^3, chest X-ray showed a homogeneous thick shadow throughout the right upper lung, and this lesion was subsequently shown as a huge fungus ball-like shadow, with a peripheral crescentic cavity, the so-called mycotic lung ball (Fig. 1). Transbronchial lung biopsy of this ball lesion proved aspergillus infection. A computed tomography scan confirmed that a branch of the right bronchus was linked to the crescentic cavity surrounding the core lesion (Fig. 2); therefore, direct transbronchial infusion of the antifungal drug, miconazole (10 mg) was performed. Subsequently, the patient frequently discharged sputa containing aspergillus colonies. The lung ball lesion rapidly shrank (Fig. 3); 1 month after the transbronchial treatment, this abnormal core shadow had disappeared from the chest X-ray, and her serum level of β-D-glucan had decreased to the normal range. At this time, the total dose of AmB received was 2.5 g and her neutrophil count was around 5000/mm^3. She was able to receive the regular consolidation and maintenance chemotherapy.

Discussion

IPA is the most severe form of aspergillus infection and has become an increasingly frequent complication in patients with acute leukemia receiving intensive chemotherapy.[1,2] The early diagnosis of IPA in this clinical setting is difficult, and the diagnosis is often made at autopsy.[3] Although the introduction of early empirical high-dose AmB administration has improved the prognosis of this fungal infection, delays in antileukemic treatment may invite the regrowth of leukemic cells, even if the induction of leukemia into complete remission is successful.[4] Therefore, we need to resolve the fungal disease as soon as possible. A radiographic sign of air crescent formation is regarded as an important diagnostic finding in IPA.[5] The pathogenesis of air crescent formation in IPA is significantly different from that of the chronic fungus ball in a preexisting old tuberculosis (TB) cavity. It is reported that the increased numbers of normal neutrophils after recovery of bone marrow function surround the fungal lesion, and proteolytic enzymes and/or free radicals released by the neutrophils break down the peripheral lesion.[6] As the result of this, air crescents form, surrounding the core lesion; it looks like a chronic fungus ball and is called a "mycotic lung ball".[7] This phenomenon, however, may be advantageous for the treamtent of IPA, because we can directly administe an antifungal drug into this cavity, either transbronchially or percutaneously.

In our patient, because her bone marrow function had recovered, and a connecting route between the bronchus and the cavity was detected by computed tomography, we

could inject miconazole directly through the connecting route into this cavity, using bronchoscopy. A short time after this treatment, the fungal lesion rapidly shrank, and disappeared. Although there have been many reports regarding the direct instillation of an antifungal drug for treating a fungus ball in an old TB cavity,[8] little is known about such therapy in the treatment of IPA in leukemic patients, probably because invasive procedures are prohibited unless the thrombocytopenia that is present after intensive chemotherapy is alleviated. Intravenous AmB administration is a standard therapy for IPA. Experimental data have revealed that combination therapy of AmB and itraconazole for aspergillosis had antagonistic results or was ineffective.[9] However, recently, this combination therapy for IPA has been reported to be effective clinically,[10] and we therefore adopted this therapy. In our patient, this treatment was considered have been effective in preventing systemic progression of IPA. In addition, the recovered neutrophils affected the fungal lesion, forming a peripheral cavity, as mentioned above. As we believed that drug delivery to the ball lesion would have been impaired after the formation of the cavity, we decided on a direct infusion of an antifungal drug. We selected miconazole for this treatment because the daily dose of AmB was almost at the maximum level, and because aspergillus is not sensitive to fluconazole. Initially, we believed that several direct injections of miconazole would be needed but only one injection led to dramatical resolution of the fungal lesion. In order to shorten the duration of treatment for IPA in leukemic patients, the intracavitary instillation of an antifungal agent is worthwhile, if clinical conditions permit.

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