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CASE REPORT

Complete heart block in a neutropenic patient with invasive aspergillosis

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ABSTRACT

A patient with leukemia who developed complete heart block after the diagnosis of pulmonary aspergillosis is reported. The patient had probable invasive pulmonary aspergillosis with a sudden tachypnea, dyspnea, fever, bilateral pulmonary infiltrates and acute respiratory insufficiency after chemotherapy. On the sixth day of antifungal therapy, she developed complete atrioventricular block. Complete heart block has not been reported during liposomal amphotericin B (LAMB) therapy. Local or hematogenous involvement of the myocardium with aspergillosis may be the most likely explanation of the complete heart block.

Key Words: Invasive pulmonary aspergillosis, complete heart block

ÖZET

İnvaziv aspergillozisli nötropenik bir hastada komplet kalp bloğu

Lösemi tanısıyla takip edilen ve pulmoner aspergillozis seyrinde tam kalp bloğu gelişen bir vaka bildirilmiştir. Kemoterapi sonrası nötropenik dönemde, ani gelişen takipne, dispne, ateş, bilateral akciğerlerde infiltrasyon ve solunum yetmezliği tablosundaki hastaya olası pulmoner aspergillozis teşhisi konmuştur. Antifungal tedavinin altıncı gününde tam atrioventriküler blok gelişmiştir. Lipozomal Amfoterisin-B tedavisi sırasında tam kalp bloğu bildirilmemiştir. Hastamızda Aspergillozis'in lokal veya hematojen yayılımı sonrası miyokard tutulumunun, tam kalp bloğunun en olası sebebi olabileceği düşünülmüştür.

Anahtar Sözcükler: İnvaziv pulmoner Aspergillozis, tam kalp bloğu

INTRODUCTION

Invasive fungal infections (IFIs) are the most important infectious causes of morbidity and mortality among immunocompromised patients. Aspergillosis is the second most common IFI with a 49% case fatality rate in leukemia-lymphoma patients [1], and lungs are the most commonly affected site. Pulmonary involvement can be local or diffuse, and invasion of major pulmonary arteries, chest wall and pericardium can result in high morbidity and mortality. Antifungal agents and surgery are the major therapeutic options in patients with invasive pulmonary aspergillosis (IPA), but because of the accompanying thrombocytopenia and poor general condition of the patients, surgery is generally difficult to apply. Amphotericin B deoxycholate (AmB-d) has been used for the treatment of IPA, but its usage is limited by its potential serious adverse effects [2]. Lipid formulations of this drug have fewer side effects and higher doses can be administered [3]. A new triazole, voriconazole, has emerged as the treatment of choice for IPA and is currently the most effective antifungal agent in the treatment of aspergillus infections [4]. Echinocandins also have some activity against aspergillosis, and caspofungin was approved for the salvage treatment of invasive aspergillosis [5]. Here we report a leukemia patient with invasive aspergillosis who developed complete heart block (CHB) after the diagnosis of pulmonary aspergillosis during antifungal treatment. Local or hematogenous involvement of the myocardium with aspergillus may be the most likely explanation of the CHB, although there was no obvious pericardial or myocardial involvement in high resolution thorax computed tomography (CT).

CASE REPORT

A 33-year-old woman was referred to the Hematology Department of Marmara University Hospital in May 2003 with a history of gum and nose bleeding, fatigue, weight loss and arthralgia. She was diagnosed as L1 type, CALLA (+) B cell acute lymphoblastic leukemia (ALL). Cytogenetic examination of bone marrow revealed 98% (+) bcr/abl. Hyper-CVAD chemotherapy regimen was planned to be given for eight cycles. After two cycles of chemotherapy her leukocyte count was still 200,000/mm^3 and peripheral blood smear showed 92% blasts. Because we could not obtain a remission with hyper-CVAD, FLAG protocol was started. The patient developed neutropenic fever on the third day of the chemotherapy. The physical examination was unremarkable and empirical anti-biotherapy with cefepime and amikacin was started. Although there was a decrease in her temperature and improvement in her general condition, she developed sudden tachypnea, dyspnea, fever, bilateral pulmonary infiltrates and acute respiratory insufficiency on the sixteenth day of antimicrobial therapy. Blood, urine and nasopharyngeal swab cultures were negative. On the same day of acute respiratory distress, meropenem therapy was started and pulmonary CT scan was performed which showed bilateral diffuse pulmonary infiltrations suggesting fungal or bacterial pneumonia. After performing bronchoscopy and bronchoalveolar lavage (BAL), 45 mg of AmB-d (1 mg/kg) was started intravenously at a constant rate of infusion over four hours. On the second day of antifungal therapy, AmB was stopped due to infusion-related fever and rigors and liposomal amphotericin B (L-AMB) was started at a dose of 3 mg/kg. She developed bradycardia and hypotension on the fourth day of treatment. The ECG showed complete atrioventricular (AV) block.

During that time, serum potassium, sodium and calcium concentrations were normal. At the time of complete AV block, she had been receiving amikacin 1 g/day for more than two weeks, levonorgestrel for 23 days, meropenem for 8 days, L-AMB for 4 days and lansoprazole for 25 days. After the development of AV block, amikacin, meropenem, levonorgestrel, and lansoprazole therapies were discontinued because of concerns about cardiotoxicity and only L-AMB was continued. On the seventh day of L-AMB treatment, *Aspergillus flavus* was isolated in BAL cultures. Later L-AMB was replaced with itraconazole, since the lipid fraction of L-AMB could be the causative agent of the AV block. Under itraconazole therapy her block did not improve. During this time her leukocyte count was 22,800/mm^3 and peripheral blood smear showed blasts suggesting refractory ALL. On the seventeenth day of AV block, the patient developed sudden hemoptysis and cardiopulmonary arrest. In spite of cardiopulmonary resuscitation, she died on the 42nd hospital day.

DISCUSSION

Aspergillus and *Candida* species are the most common fungal pathogens among patients with prolonged and profound neutropenia caused by chemotherapy. Despite perceived advances in current treatment, invasive aspergillosis still remains a devastating opportunistic infection

among neutropenic patients, and the mortality rates may approach 100% with invasive aspergillosis [6,7]. Cardiac involvement by aspergillus is very rare and it may result from contagious spread from the lungs or from hematogenous spread. Arrhythmias can develop due to pericarditis or myocarditis.

Pericardial and myocardial aspergillosis are rare manifestations of systemic aspergillosis. Most cardiovascular aspergillus infections occur as a post-surgical complication or as an infection of prosthetic valves. Most involve mitral or aortic valves where masses of infected thrombotic tissue may obstruct the orifice [8]. In one case report, a patient who underwent bone marrow transplantation for acute myeloid leukemia developed IPA during induction chemotherapy. The symptoms of IPA were aggravated following neutrophil and monocyte recovery. The patient died of sinus arrest due to complete AV block 31 days after his transplant. At autopsy, it was found that the fungus had invaded the myocardium, including the sinoatrial conduction system [9]. In another case report, two patients with cardiac aspergillosis who presented with arrhythmia during therapy of acute leukemia were reported; one had myocardial infarction with complete AV block [10]. Another report described invasive pulmonary aspergillosis complicated by complete AV block and aspergillus pericarditis after induction chemotherapy for ALL [11]. Our patient had probable invasive pulmonary aspergillosis (according to recent EORTC-MSG criteria) with a sudden tachypnea, dyspnea, fever, bilateral pulmonary infiltrates and acute respiratory insufficiency after chemotherapy.

Although there was a decrease in her temperature after initiation of antifungal therapy, her general condition did not improve. On the sixth day of antifungal therapy, she developed bradycardia, hypotension and complete AV block. When the CHB developed, she had been receiving many drugs so we initially stopped all the drugs which could cause cardiotoxicity except L-AMB. We also searched the literature about cardiac side effects of L-AMB. Acute cardiac events have not been reported during the first dose of L-AMB infusion. Ventricular fibrillation and fatal cardiac arrest during the seventh dose of L-AMB has been reported in only one patient [12]. CHB has not been reported during L-AMB therapy. Her pulmonary high resolution CT showed pulmonary lesions which were very close to the pericardium, but we could not see a clear pericardial invasion. There was also no clinical sign of pericardial involvement. The patient's general condition did not improve and she died on the seventeenth day of CHB because of massive hemoptysis and cardiac arrest which is suggestive of progressive IPA. Since permission for a post-mortem examination was not provided by the family, we were unable to show possible cardiac fungal involvement that could be responsible for the CHB in our patient.

Here we present an IPA patient who developed resistant CHB during pulmonary aspergillosis. Based on the guidance of previous literature, this condition in our patient can be explained either by local or systemic dissemination of aspergillosis. It is not clear whether L-AMB itself could cause such an arrhythmia and there is no data in the literature supporting this idea.

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