□ CASE REPORT □

Myocardial Infarction Caused by Aspergillus Embolization in a Patient with Aplastic Anemia

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Abstract

A 38-year-old Japanese man with severe aplastic anemia had invasive pulmonary aspergillosis as a complication. He was treated with amphotericin B for six weeks, but the aspergillosis did not improve. Then he experienced a fatal myocardial infarction. An autopsy revealed disseminated aspergillosis involving pericarditis and Aspergillus embolization to the coronary arteries. This led to the acute myocardial infarction. Cardiac aspergillosis is rare, but should be included within the differential diagnosis when chest pain of unknown origin occurs in an immunosuppressed patient.

Key words: aplastic anemia, pericarditis, myocarditis, myocardial infarction, Aspergillus

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Introduction

Disseminated aspergillosis often occurs in immunosuppressed patients and has increased in frequency in recent years. Cardiac involvement of aspergillosis, including myocardial infarction, pericarditis and myocarditis, is comparatively rare. Myocardial infarction secondary to Aspergillus embolization to the coronary arteries has been reported in several patients (1-6), and Aspergillus pericarditis and myocarditis have also been described in some papers (7-17). In this report, we describe a case in an aplastic anemia patient with fungal occlusion of the coronary arteries and fungal invasion of the pericardium and myocardium, although he had been receiving treatment with amphotericin B.

Case Report

A 38-year-old Japanese man was diagnosed with severe aplastic anemia and hospitalized on February 28, 2000. His bone marrow was characterized by severe hypoplasia. He had undergone a left nephrectomy during childhood. Hematologic findings at diagnosis were white blood cells (WBC)

$0.8 \times 10^9/l$ with 0% neutrophils, 95% lymphocytes, and 5% monocytes; platelets were $49 \times 10^9/l$ and hemoglobin 11.6 g/dl. The bone marrow was severely hypocellular with 78.4% lymphocytes, and 14.4% plasmacytes. He was treated with cyclosporin A, granulocyte colony-stimulating factor, corticosteroids and antithymocyte globulin, but they had no effect. The peripheral neutrophil count was zero or less than $0.1 \times 10^9/l$ throughout his clinical course. Erythrocyte and platelet transfusions were frequently necessary. He did not have an HLA-matched sibling. He had pyrexia and cough during mid-March 2000. Serum C-reactive protein was at an aberrantly high level (more than 20 mg/dl). His chest X-ray showed pulmonary infiltration of the left lower lobe. Despite treatment with broad-spectrum antibiotics, pneumonia worsened. On March 27, 2000, amphotericin B (0.5 mg/kg/day) was started intravenously because a test for serum Aspergillus antigen was positive and beta-D glucan had increased from <11 to 18.7 pg/ml, but his pneumonia did not improve. A fungus ball was visible in the left lower lobe on a chest X-ray. On April 18, 2000, the dosage of amphotericin B was increased (0.7 mg/kg/day), but his pneumonia worsened.

On May 5, 2000, he suddenly complained of anterior chest pain. The pain was somewhat relieved by sublingual

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administration of nitroglycerin. An electrocardiogram revealed ST elevation in leads I and aV_L, and his serum creatine phosphokinase level rose to 256 IU/l. Emergency coronary angiography showed total occlusion of the left anterior descending branch (first diagonal branch: #9), and myocardial infarction was diagnosed. Percutaneous transluminal coronary angioplasty (PTCA) was attempted, but it was unsuccessful because the coronary embolization was too solid. The condition of the patient was stable after PTCA was attempted. On May 10, 2000, he suddenly went into cardiac and respiratory arrest. Cardiopulmonary resuscitation was attempted, but he died.

An autopsy revealed the presence of disseminated aspergillosis, involving the lungs, heart and brain. Microscopic examination showed Grocott-Gomori methenamine-silver nitrate stain positive and dichotomously branching hyphae of *Aspergillus* (Fig. 1). The largest *Aspergillus* infection focus, with a diameter of seven centimeters, was present in the superior lobe of the left lung. Severe left pulmonary infarction due to direct arteriovenous fungal invasion and disseminated bilateral fungal pneumonia extending to the pleura, pericardium and ribs were found. Myocardial infarction was observed. The diagonal branch of the left coronary artery was occluded by hematogenous *Aspergillus* embolizations, and a transmural infarction was present in the anterior wall of the left ventricle. Furthermore, pulmonary aspergillosis had directly invaded the epicardium and myocardium. Widespread fibrinous pyopericarditis was observed, and extensive multifocal areas of myocardial necrosis due to fungal plugs were also present. The hyphae had reached the intracardiac lumen. In addition, fungal vegetation was found on the occipital lobe of the left brain.

Discussion

Various infections become complicated by severe immunosuppression due to hematological disorders and immunosuppressive therapies. Disseminated aspergillosis occurs in immunocompromised hosts. In particular, cardiac aspergillosis is one of the most serious complications of systemic aspergillosis. Cardiac aspergillosis has been encountered as a complication in patients after cardiovascular surgery, but it is rare in patients with no history of cardiac surgery (7). It is divided broadly into two categories: direct *Aspergillus* invasion and *Aspergillus* embolization. Various clinical symptoms have been reported, including myocardial infarction (1-6), myocarditis (6-10), endocarditis (7, 18-22), pericarditis (7, 8, 10-17), pericardial tamponade (11, 13, 16), superior vena cava syndrome (23), aortitis (24), intracardiac mass (25) and atrioventricular block (9).

Myocardial infarction due to *Aspergillus* embolization often becomes a problem in the differential diagnosis with common myocardial infarction. For hemodynamic reasons, an embolic event is likely to engage the descending branch of the left coronary artery (1). Generally speaking, in these cases, it is very difficult to diagnose these symptoms as *As-*

Figure 1. (A) Cross-section of the coronary artery of a patient with a thrombus occluding the artery (Grocott-Gomori methenamine-silver nitrate staining; $\times 40$). (B) High-power views of the section from (A), showing invasion of aspergillus (Grocott-Gomori methenamine-silver nitrate staining; $\times 400$).

pergillus (26). Furthermore, treatment for cardiac aspergillosis is very difficult, even when accurately diagnosed. Cardiac aspergillosis is rarely diagnosed before death, and it is fatal. Amphotericin B (with or without 5-flucytosine), itraconazole and surgical procedures are chosen for treatment (6, 11, 12, 16, 27). Treatment has been successful in a few cases (12, 16, 28), but most patients have died. Cultures of various specimens, chest X-rays and serological assays are used for diagnosis, but they are often inferior in sensitivity and specificity (29). Some reports suggest that the polymerase chain reaction assay (22, 30, 31) and the enzyme-linked immunosorbent assay (32) are useful for diagnosis. Walsh et al reported that pulmonary aspergillosis preceded development of pericarditis (13). In the present case, the patient had been neutropenic for a few months prior to the onset of cardiac problems, but he had no cardiac problems before this episode. He had no history of cardiac surgery, and he had few risk factors (smoking, hypertension, diabetes, hyperlipidemia, familiar history, and so on) of myocardial infarction except for slight obesity. We made a diagnosis of *Aspergillus* infection before his death based on a pneumonia image on a chest X-ray and a positive serum *Aspergillus* an-

tigen finding. Thereafter we administered amphotericin B. We had wanted to administer a larger quantity (1.0-1.5 mg/kg/day) of amphotericin B to the patient, but we were unable to because he had only one kidney and his renal function was not adequate. Therefore we used an insufficient quantity (0.5 - 0.7 mg/kg/day) of amphotericin B. We could not use other antifungal drugs because of drug eruption. Unfortunately, the onset of myocarditis and myocardial infarction could not be prevented. Supplementarily, we tried cultures of sputum, blood and autopsy specimens, but we could not identify which *Aspergillus* species was involved. *Aspergillus fumigatus* antigen was negative.

The spread of the *Aspergillus* infection to the patient's heart appears to have been by both hematogenous spread from the involved pulmonary veins and direct invasion from pulmonary aspergillosis. There have been several published cases of cardiac aspergillosis, and myocardial infarction caused by *Aspergillus* embolization to the coronary arteries has been reported by several authors. In the present case, we considered that the patient died of myocardial infarction as well. In addition, he had complicated myocarditis due to direct infiltration from *Aspergillus* pneumonia to the cardiac muscle. Generally, when patients with a severe immunosup-

pressed condition, such as in the present case, have an *Aspergillus* infection, it may be difficult to cure aspergillosis even if it is treated aggressively (10, 11). However, empirical use of amphotericin B should be initiated if the immunocompromised patient has a persistent fever and antibiotics have been ineffective (33). Prevention of fungal infection from the early stage, early diagnosis using various diagnostic procedures and early initiation of therapy are very important (1). Recently, new antifungal agents for the treatment of aspergillosis have become available: caspofungin (34), micafungin (35) and voriconazole (36). These drugs have potent antifungal action including action against *Aspergillus*. Herbrecht et al reported that voriconazole is more effective and has fewer side effects than amphotericin B in patients with invasive aspergillosis (36). Maertens et al showed that caspofungin is useful in the salvage treatment of invasive aspergillosis (34). These drugs are expected as a new treatment strategy for aspergillosis.

It is difficult to treat systemic aspergillosis, but we should attempt to detect the symptoms of pulmonary aspergillosis, pericarditis and myocardial infarction as soon as possible, and cardiac aspergillosis should be suspected in such a situation.

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