Systemic Aspergillosis as Cause of Myocardial Infarction

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Systemic aspergillosis is encountered with increasing prevalence in immunocompromised patients undergoing chemotherapy. The current communication describes the clinical and postmortem findings in three leukemic patients who developed myocardial infarction secondary to Aspergillus embolization of the coronary arteries. They were all immunosuppressed owing to previous chemotherapy and had been treated for suspected fungal infection with amphotericin B (0.6 mg/kg) for at least 1 week prior to this episode. It is postulated that the infection was spread through the blood since in all three cases the descending branch of the left coronary artery was occluded. Heart involvement resulting from fungal infection should be suspected when chest symptoms of unknown origin occur in this patient population.


SYSTEMIC ASPERGILLOSIS HAS BEEN ENCOUNTERED with increasing frequency in patients with malignant disease who are undergoing chemotherapy.¹-³ This increasing occurrence has been ascribed to impaired host defense mechanisms resulting from the disease itself and from immunosuppressive therapy paired with improved supportive care.²,⁴,³ A positive diagnosis of aspergillosis is infrequently made clinically, and amphotericin B is advocated as the therapy of choice, albeit with limited effect in most patients.⁶-⁹ Pericarditis secondary to Aspergillus invasion of the pericardial sac has been described in a few patients,¹⁰-¹² and involvement of the myocardium alone or in combination with endocardial or pericardial invasion has also recently been described.¹³ In this report, we describe three leukemic patients who developed acute myocardial infarction secondary to Aspergillus embolization of the coronary arteries. All patients developed this complication while receiving treatment with amphotericin B. These cases emphasize that myocardial infarction should be included in the differential diagnostic workup for chest pain of unclear origin in immunocompromised patients who are at high risk for systemic aspergillosis.

Case Reports

Case 1

A 48-year-old white woman was diagnosed as having acute myeloid leukemia. She attained complete remission after two courses of Adriamycin (doxorubicin), cytarabine (Ara-C), 6-thioguanine, prednisone, and vincristine and remained in complete remission for a year with monthly maintenance courses of Ara-C, vincristine, and prednisone. Upon relapse, a second complete remission was attained with 6-thioguanine, Ara-C, and daunorubicin. This remission lasted for another year, after which she again relapsed. Reinduction attempts with amsacrine (m-AMSA) and cisplatin were unsuccessful, and the decision was made to treat her with a high-dose chemotherapy regimen of cyclophosphamide, Carmustine, and etoposide followed by autologous bone marrow rescue. After she recovered from the high-dose treatment, the patient's bone marrow was still leukemic, and new reinduction attempts were made with one course of low-dose Ara-C followed by a course of bisantrene, without definite antileukemic effect. The therapy was changed to high-dose Ara-C¹⁴ for two consecutive courses. During this time, the patient was persistently febrile, but no source of infection was found. The second course of Ara-C was administered under steroid coverage to prevent pulmonary toxicity.¹⁵ On day 4 of the second course of high-dose Ara-C, the patient complained of chest pain. Physical examination revealed a pericardial rub. A chest x-ray revealed early pneumonia and an electrocardiogram (ECG) showed low voltage throughout the leads and QRS complex changes compatible with myocardial infarction. The pericardial rub and chest pain improved over the next 24 hours with steroid treatment, and the steroid doses were gradually reduced over the following week. The patient remained febrile and was treated with broad-spectrum antibiotics and amphotericin B. Her condition gradually deteriorated, with ensuing respiratory failure that necessitated intubation and mechanical ventilation. One week after the onset of chest pain, the patient's chest x-ray showed signs of fungal pneumonia¹⁶ that had developed during treatment with amphotericin B (0.6 mg/kg/day). Investigational treatment with liposome-encapsulated amphotericin B was started,¹⁷ but the patient subsequently developed cardiogenic shock and hypotension secondary to a myocardial infarction and died. Autopsy showed severe bilateral fungal pneumonia extending to the pleura, peritoneum, and pericardium. There was a large mural fungal thrombus in the mainstem of the pulmonary artery.
and the pulmonary veins were invaded by Aspergillus. Infarcts secondary to fungus-containing emboli were encountered in several of the smaller splenic arteries. The anterior descending and marginal branches of the left coronary artery were occluded by fungal emboli with subsequent infarction of the anterolateral and posterior walls of the left ventricle (Fig. 1).

Case 2

A 32-year-old white male presented in 1968 with acute lymphocytic leukemia. He achieved complete remission with vincristine, prednisone, and methotrexate. Maintenance therapy was given until 1973. In 1976, the patient had a relapse, and complete remission was reinduced with Adriamycin and ifosfamide. Cyclic maintenance therapy was continued until 1979. In 1980, the patient had a second relapse that responded to chemotherapy. At this time, he was also diagnosed as having chronic active hepatitis. In July 1983, he was found to have a third relapse and was again induced into complete remission with methotrexate, L-asparaginase, and prednisone. While in complete remission he received an allogeneic bone marrow transplant from an HLA-compatible sister. In the early posttransplant period, the patient developed fever and respiratory failure, and his chest x-ray showed bilateral pulmonary infiltrates. Despite treatment with broad-spectrum antibiotics, the apparent pneumonia worsened, and empiric amphotericin B treatment was started, together with leukocyte transfusions. Owing to progressive respiratory failure, the patient had to be intubated and mechanically ventilated. An ECG on day 14 showed changes compatible with an anterolateral wall myocardial infarction. In spite of vigorous supportive care, the patient’s condition gradually deteriorated. On day 35 after the transplant, he developed rapid atrial fibrillation, became hypotensive, and suffered a cardiac arrest. Autopsy revealed extensive fungal pneumonia extending to the pleural cavities, and with invasion of fungal organisms into the pulmonary veins. The heart had endocarditis changes with vegetations on all four valves, however without microscopic evidence of fungal organisms. An Aspergillus containing embolus occluded the anterior descending branch of the left coronary artery (Figs. 2 and 3), causing infarction of a large part of the anterior wall of the left ventricle.

Case 3

A 21-year-old woman presented with acute myeloid leukemia. Chemotherapy was initiated with m-AMSA, Ara-C, vincristine, and prednisone. She did not respond, and since she had an HLA-identical brother, she received an allogeneic bone marrow transplant after conditioning with piperazinedione and total body irradiation. When the patient recovered, her bone marrow was still leukemic and she was now treated with two courses of high-dose Ara-C. The first course was complicated by an episode of septicemia and pericarditis, and treatment with broad-spectrum antibiotics, amphotericin B (0.6 mg/kg/day), and steroids...
was implemented. After the second course of Ara-C, the patient developed a generalized encephalopathy with grand mal seizures and progressive liver failure. On the final day of her life, she suddenly became hypotensive. She did not respond to dopamine and fluids, became anuric and died. Autopsy revealed extensive pulmonary edema with *Aspergillus* growth that had caused infarction of pulmonary tissue, and fungal organisms were invading the pulmonary veins. The brain had infarcted areas in the basal ganglia secondary to *Aspergillus* embolization of the arteries in the skull base. In the heart, the anterior left ventricular wall had an approximately 3.5 cm × 5 cm transmural lesion with infarction and hemorrhage secondary to fungal occlusion of one descending branch of the left coronary artery (Fig. 4).

**Discussion**

Systemic aspergillosis is encountered with increasing frequency in the immunocompromised patient population to which all of our patients belonged. The three patients described above had been neutropenic for several weeks prior to the onset of cardiac problems. The great difficulty in diagnosing systemic fungal infections has supported the empiric use of amphotericin B in granulocytopenic patients with persistent fever. The current cases demonstrate development of myocardial infarction despite administration of amphotericin B for more than 1 week (Table 1). None of the patients had a history of cardiac problems, although two of them had had an episode of pericardial rub before developing a myocardial infarction. Fungal pericarditis has been reported as an uncommon, but potentially lethal, event in similar clinical settings, and it is possible that the rub was an early sign of systemic aspergillosis in these patients. However, at autopsy, the *Aspergillus* did not appear to have spread from the pericardial sac through direct extension to the myocardium but rather through hematogenous dissemination to the coronary arteries, since there were definite embolic masses in the lumina of the coronary arteries. For hemodynamic reasons, an embolic event is likely to engage the descending branch of the left coronary artery. The source of the emboli was most likely the pulmonary veins, since they were invaded by fungal organisms in all
three cases. Systemic aspergillosis needs to be considered as a possible cause of myocardial infarction in this patient population. Once myocardial infarction appeared, a rapidly deteriorating course followed in all our patients. Early identification of and therapy for the symptoms of pulmonary aspergillosis, pericarditis, and, subsequently, myocardial infarction, are very important; successful therapy of pulmonary aspergillosis with amphotericin B alone or in combination with leukocyte transfusions in immunocompromised patients has been reported, even though systemic aspergillosis is difficult to treat. All our patients were treated with amphotericin B empirically before the onset of chest symptoms, indicating suboptimal control of the infection with amphotericin B alone. The addition of granulocyte transfusions has shown effect against fungal infections, and addition of either rifampin or 5-fluorocytosine should be considered for disseminated aspergillosis.

REFERENCES


<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of neutropenia* (days)</th>
<th>Physical symptoms and signs</th>
<th>ECG</th>
<th>Fungal invasion of pulmonary veins on autopsy</th>
<th>Duration of amphotericin B Prior to MI</th>
<th>Fungal cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>118</td>
<td>Chest pain, fever, pericardial rub, chest pain (14 days prior to demise), last day of life sudden hypotensive shock</td>
<td>At onset of chest pain—low voltage pathol R-wave progression; last day of life anterolateral MI</td>
<td>Yes</td>
<td>0.6 mg/kg BW daily for 7 days prior to onset of chest pain</td>
<td>Aspergillus in pleural fluid 4 days prior to death, mold in sputum 2 days prior to death</td>
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<td>2</td>
<td>17</td>
<td>Fever, basilar pneumonia and pleural effusions progressive over 1 wk prior to MI</td>
<td>Day 14 posttransplant symptoms of anterolateral MI</td>
<td>Yes</td>
<td>0.6 mg/kg BW daily for 7 days prior to ECG-proven MI</td>
<td>All cultures negative</td>
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<tr>
<td>3</td>
<td>21</td>
<td>Fever, transient pericardial rub</td>
<td>No sign of myocardial process</td>
<td>Yes</td>
<td>0.6 mg/kg BW daily for 18 days prior to death</td>
<td>All cultures negative</td>
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</tbody>
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Neutropenia (500 polys/mm³) prior to cardiac symptomatology. MI: myocardial infarction.

BW: body weight.