Fatal Myocardial Aspergillosis in an Immunosuppressed Child

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Abstract: A girl with resistant acute myeloid leukemia (AML) had a stem cell transplantation. Preceding transplantation, she had recurrent pneumonitis. No causative agent was identified. Despite several antibiotics including high-dose liposomal amphotericin-B, pulmonary infection progressed. Aspergillosis, always considered, could not be documented. She died from cardiac arrest on the second day after transplantation, with no forewarning of previous heart disease. Pericardial and myocardial aspergillosis was an autopsy finding. Pericardial and myocardial aspergillosis, rare manifestations of systemic aspergillosis, should be considered in any immunocompromised patient with long-lasting pulmonary infection, even in the absence of specific cardiac findings.

Key Words: Myocardial aspergillosis—Stem cell transplantation.

Aspergillus infection is a life-threatening complication of stem cell transplantation (SCT). The prolonged aplasia and immunosuppression before and after SCT render the patients extremely vulnerable to invasive infectious diseases. We report a patient who died soon after SCT because of Aspergillus pericarditis with focal myocardial and endocardial involvement caused by direct spread from pulmonary aspergillosis.

CASE REPORT

Six months of chemotherapy using the acute myeloid leukemia Pediatric Oncology Group protocol (POG 9421) (1) (cytosine arabinoside, etoposide, mitoxantrone, daunorubicin, cyclosporine, 6-thioguanine, intrathecal cytosine arabinoside) failed to induce a sustained remission in a 6 1/2-year-old girl with acute myeloid leukemia-M2. During this period, the patient had several infectious complications attributed to the immunosuppression and recurrent profound neutropenia episodes: Streptococcus pseudodiphtheriae and Stomatococcus mucilaginosus septicemias, and from the fourth month on, recurrent pneumonitis episodes with accompanying pleuritis. The x-rays showed interstitial pneumonitis, a diffuse accentuation of the bronchial tree, and subsequently, a retrocardiac density. A bone marrow aspiration performed at the end of the fifth month revealed 32% leukemic cells. Despite the continuation of chemotherapy, bone marrow at the end of the sixth month of treatment showed persistence of 28% of blasts. Chemotherapy was, therefore, not stopped in the presence of the lung infection, and the patient was to ultimately undergo transplantation with stem cells from a partially histocompatible (4/6 human leukocyte antigen-compatible) unrelated cord blood. Two bronchoalveolar lavages and a pleural fluid aspiration revealed neither infectious agents nor malignant cells. Repeated blood, urine, and respiratory secretion cultures were also noncontributive. No computed tomography scan was performed. The pneumonitis episodes were treated with diverse, large-spectrum antibiotics, to which liposomal amphotericin-B (AmBisome; Nexstar, San Dimas, CA, U.S.A.) at a dose of 8 mg/kg per day was added 2 months after the beginning of pulmonary infection, i.e., in the sixth month of chemotherapy. It was stopped 1 month before the conditioning because of improvement in clinical (fever disappearance) and radiologic findings and of nephrotoxicity. It was reintroduced 2 weeks before the conditioning because of fever, tachypnea, interstitial pneumonitis on x-rays, and increased C-reactive protein. There were no signs of cardiac disease except for tachycardia, which was attributed to fever, ongoing pulmonary infection, and excessive fluid intake. The echocardiogram revealed a mildly dilated but well-functioning left ventricle; there was no pericardial fluid. The serial chest x-rays performed on the days preceding the conditioning showed a decrease in the pulmonary infiltrates. Computed tomography scan of the lungs or sinuses was not performed because of clinical and radiologic improvement.

During the conditioning regimen, fever reappeared, along with tachycardia (120–140/min), tachypnea (44/min) with oxygen dependency (3 L/min). The pulmonary infiltrates progressed with near-complete opacification of the left lung. Cardiac auscultation and blood pressures (110/50 mmHg) remained normal on the day of SCT. On the second day after SCT, the patient had a brief cardiac arrhythmia that developed into a cardiac arrest; resuscitation attempts, started immediately, were unsuccessful. Autopsy revealed invasive pulmonary aspergillosis in both lower lobes accompanied by local pleuritis (Fig. 1) and massive pericar-
dial aspergillosis focally extending to the myocardium (Fig. 2) and in the left atrium to the endocardium.

**DISCUSSION**

*Aspergillus* infection, although strongly suspected, could never be documented in the patient despite several broncho-alveolar lavages and pleural fluid aspirations, as well as blood, urine, and respiratory secretion cultures. There were no clinical and echographic signs of cardiac insufficiency except for tachycardia, which was attributed to fever, volume overload, and the ongoing pulmonary infection. However, despite the lack of diagnostic evidence, in the context of an immunocompromised host with neutropenia, she received high doses of liposomal amphotericin-B for several weeks before SCT.

The patient’s prognosis was compromised because she was in relapse with aggressive disease and had to be conditioned immediately after the final chemotherapy course. The pulmonary infiltration progressed already during the conditioning phase. The particular localizations of the pulmonary foci discovered only at autopsy led to contiguous cardiac invasion. Pericardial aspergillosis was not suspected earlier because of the absence of clinical signs and normal echocardiographic findings except for a mild ventricular dilatation before conditioning. Death was attributed to deadly arrhythmia resulting from infiltration of the myocardium by hyphae.

Invasive aspergillosis of any organ system is commonly considered as a contraindication for bone marrow transplantation or SCT. However, we have successfully transplanted bone marrow in two children without malignancy (chronic granulomatous disease, severe aplastic anemia) who had invasive but noncardiac aspergillosis diagnosed before bone marrow transplantation. These children received liposomal amphotericin-B, granulocyte-colony stimulating factor-stimulated granulocyte-transfusions, and one underwent surgery (2,3). Granulocyte transfusions should be considered seriously in these profoundly immunocompromised patients with life-threatening infections (2,4). Had we made the diagnosis of pulmonary aspergillosis, we would have administered granulocyte-colony stimulating factor-stimulated granulocyte transfusions and surgical pulmonary intervention in addition to liposomal amphotericin-B before SCT. However, by delaying SCT, the patient would probably have died from leukemia progression. Although invasive aspergillosis is a well-known infectious complication of immunosuppression with prolonged profound neutropenia (5), there are few published pediatric cases of cardiac aspergillosis (6–9). These are summarized in Table 1. In adults and children, pericardial aspergillosis is rarely diagnosed before death and even so is almost always fatal (5,10). The most recent report of an adult with acute lymphoblastic leukemia surviving pericardial aspergillosis was published in 1998 by Le Moing et al., with an extensive review of the literature (10). In this review, of the 29 evaluable patients with pericardial aspergillosis, 72% had underlying malignancy and in only 21% were cultures
contributive. Clinical, radiologic, ultrasonographic, or elec-
trocardiographic signs of cardiac involvement were re-
ported in 62% (18/29). Sixty-six percent of the patients had
received antifungal treatment, but only four survived. In
three of those patients, medical treatment was combined
with aggressive surgical intervention, and two had subacute
infection. None of the four survivors had myocardial or
endocardial involvement. Most of the patients had pulmo-
nary aspergillosis with contiguous spread to the pericar-
dium. In their extensive review of invasive aspergillosis in
2,121 published cases of which only 379 had evaluable data,
Denning and Stevens found 11 cases of pericardial asper-
gillosis (5). Of the three survivors, only one had a pericar-
dectomy. In these three patients, only pericardial involve-
ment was noted. Only 1 of the 11 was a child (with chronic
granulomatous disease), who had a fatal outcome (5,7)

<table>
<thead>
<tr>
<th>Publication year/reference</th>
<th>Patient age (y)</th>
<th>Underlying disease</th>
<th>Clinical signs of pericarditis</th>
<th>EKG signs of pericarditis</th>
<th>Other sites of aspergillosis</th>
<th>Diagnosis of aspergillosis</th>
<th>Treatment of aspergillosis</th>
<th>Outcome of aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959/6</td>
<td>13</td>
<td>Steroid therapy CGD</td>
<td>?</td>
<td>NP</td>
<td>Brain, lungs, pleura, myocardium</td>
<td>Postmortem histology + culture</td>
<td>None</td>
<td>Died, D + 16</td>
</tr>
<tr>
<td>1982/7</td>
<td>6</td>
<td>CGD</td>
<td>?</td>
<td>?</td>
<td>Brain, lungs, thyroid, kidneys, spleen</td>
<td>Biopsy, histology + culture</td>
<td>AmB 2 mg/kg per day + granulocyte transfusion</td>
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<td>1982/8</td>
<td>16</td>
<td>AML</td>
<td>NP</td>
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<td>Lungs, skin</td>
<td>Miconazole, AmB, pericardectomy Liposomal AmB 8 mg/kg per day 2 × wk, stop 2 wk, restart 8 mg/kg per day 6 × wk (until death)</td>
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<td></td>
</tr>
<tr>
<td>1999/PR</td>
<td>6.5</td>
<td>AML</td>
<td>None</td>
<td>None</td>
<td>Lungs, pleura, focal extension to myocardium and endocardium</td>
<td>Postmortem histology</td>
<td>Liposomal AmB 8 mg/kg per day 2 × wk, stop 2 wk, restart 8 mg/kg per day 6 × wk (until death)</td>
<td>Died, D + 2, after SCT</td>
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?: not described; CGD: chronic granulomatous disease; AML: acute myeloid leukemia; NP: not performed; AmB: amphotericin B; SCT: stem cell transplantation; PR: present reference.

### TABLE 1. Published pediatric cases of Aspergillus pericarditis

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REFERENCES


