Tracheoesophageal Fistula Induced by Aspergillus Infection Following Bone Marrow Transplantation

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INTRODUCTION

Invasive aspergillosis infection, a major problem in patients undergoing bone marrow transplantation (BMT), is the most common cause of fungal pneumonia and a major cause of post-BMT mortality.1–5 We report a child suffering from myelodysplastic syndrome (MDS) who developed a tracheoesophageal fistula caused by post-BMT pulmonary aspergillosis.

CASE REPORT

A 10-year-old boy was referred to the BMT department for treatment of MDS (refractory anemia with excess 20% myeloblasts). The conditioning for BMT included total lymphoid irradiation (600 rad), VP16 (1,275 mg), cyclophosphamide (1,260 mg), melphalan (51 mg) and total body irradiation (1,200 rad).

On the day of transplant (day 0) the patient received BM (8.4 × 10^8 cells/kg body weight), T-cell depleted with monoclonal antibody (rat anti-human IgG anti-CDw52) from his HLA matched sister. The course of BMT was completed by graft rejection on post-BMT day 5. A second BMT was performed with cells from the sister, but without T-cell depletion. Prior conditioning consisted of anti-thymocytic globulin for 3 days and one dose of cyclophosphamide (60 mg/kg body weight). Granulocyte macrophage colony stimulating factor (GM-CSF) and Interleukin-3 (IL3) were given post-BMT to enhance engraftment.

On day 2 after the second BMT, (57 days post first BMT) while receiving broad spectrum antibiotics (imipenem, vancomycin, amikacin) and amphotericin B (0.5 mg/kg; aspholastic dose) the patient developed fever, neutropenia, cough, inspiratory wheezing and his abdomen was distended. A day later he was in acute respiratory distress with consolidation in the right upper lobe as determined by chest radiography. Flexible fiberoptic endoscopy detected an obstruction by white material in the opening of the left main bronchus (LMB). Histopathological examination of the material, obtained by suction through the bronchoscope, revealed typical aspergillosis hyphae. No bronchial or transbronchial biopsies were carried out. A second rigid bronchoscopy was performed with suction of necrotic tissue from LMB and with infusion of amphotericin B over the white necrotic tissue. Liposomal amphotericin (4 mg/kg body weight) was initiated and the patient was extubated after 5 days.

On day 10 after the second BMT the boy had convulsions with respiratory distress and a distended abdomen. Intubation and mechanical ventilation were performed. A few hours postintubation, the nasogastric tube sac was filled with air containing a high percentage of oxygen and the abdomen was even more distended. A tracheoesophageal fistula was suspected. Flexible fiberoptic endoscopy detected extension of the necrotic tissue and several holes in the posterior wall of the lower trachea (Fig. 1). Total body computerized tomography (CT) (Fig. 2) revealed the fistula as well as a brain lesion, pleural effusion and rupture of the gall bladder. Despite elevation of the white blood cell counts and good bone marrow engraftment the patient died on day 67 after the first BMT from respiratory failure.

DISCUSSION

Acquired tracheoesophageal fistula may be caused by malignant tumors, infection with different microorganisms such as tuberculosis, actinomycosis, histoplasmosis, syphilis, and aspergillosis.6–9 Fungal infections are most common during the early post-transplant neutropenic period10 and aspergillosis is the most common cause of fungal pneumonia. The risk of infection is increased in BMT patients, especially after transplantation with T-cell-depleted bone marrow.11 Invasive aspergillosis of the lungs after BMT has a wide pathologic spectrum, namely invasion of small blood vessels leading to...
occlusion and consequently to pulmonary infarction, solitary cavitation, bronchogenic granulomas, bronchogenic obstruction, and pseudomembranous necrosis of the bronchi with or without lung involvement.\textsuperscript{12-15}

In our patient, at the early stage of disease, chest radiographs did not indicate any pulmonary process causing respiratory distress. The results of bronchoscopy and bronchoalveolar lavage led to the diagnosis of bronchial aspergillosis and tracheoesophageal fistula.

Prolonged neutropenia, caused by bone marrow rejection, facilitated development of invasive aspergillosis in this patient. The fungi penetrated the mucosa leading to obstruction of the left main bronchus and subsequently to the tracheoesophageal fistula. The fistula was noticed during high pressure mechanical ventilation. In the late course of the disease, aspergillosis was also diagnosed in the brain, liver and gall bladder. In severe immunocompromised patients, especially post-BMT, invasive aspergillosis has been documented in almost all organs, including the brain, heart, spleen and blood vessels.\textsuperscript{2,16-18}

The treatment of tracheoesophageal fistula is rapid surgical repair or insertion of an esophageal prosthesis,\textsuperscript{19} combined with specific antibiotic therapy. Recently, more specific and more effective anti-fungal drugs have been developed. Liposomal amphotericin\textsuperscript{20} and itraconazole,\textsuperscript{21} alone or in combination with conventional amphotericin, result in better clearance of aspergillosis and an improved outcome, compared with conventional amphotericin therapy alone.

Because of his poor general condition and severe thrombocytopenia, our patient was treated with liposomal amphotericin B, GM-CSF, and IL3 (for faster engraftment with no surgical intervention), without surgical intervention.

Amphotericin B and fluconazole\textsuperscript{12,22,23} fail to prevent aspergillus infection. Systemic amphotericin B, at a higher dose, is too toxic as prophylaxis. Inhalation of amphotericin B may be useful in preventing invasive pulmonary aspergillosis.\textsuperscript{24} High dose ketoconazole is effective against aspergillus infection, but is contraindi-
cated in patients receiving cyclosporine prophylaxis against graft vs. host disease. Air filtration was found to significantly reduce the number of aspergillus spores in the air and thereby reduce cases of aspergillus infection.23

Aggressive operative treatment of fungal infection of the lungs combined with anti-fungal chemotherapy may be best for localized disease.25 Despite inherent difficulties in reaching a consensus on the relative role of surgery in immunocompromised patients, selective interventions can be performed with favorable outcome.26

Early detection by routine bronchoscopy is crucial in the diagnosis and treatment of aspergillus infection,23 because some patients with pulmonary aspergillosis may have normal chest x-rays4 as a result of inadequate inflammatory response. Furthermore, bronchoalveolar lavage (BAL), a noninvasive procedure, has not been associated with mortality and has produced minimal morbidity.22 Repeated BAL with or without transbronchial biopsy can improve diagnosis (especially of aspergillus) and follow-up.5

Changing from prophylactic to therapeutic doses of amphotericin B in selected cases, combined with surgery, especially at early stages, may prevent invasive pulmonary aspergillosis infection.20,21

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