10-year-old boy developed severe dyspnea and respiratory failure during a hospitalization for an allogeneic unrelated bone marrow transplantation for acute myeloid leukemia. He had first presented 23 weeks earlier with acute myeloid leukemia and had not responded to the initial induction chemotherapy. Next, he was successfully treated with another regimen of remission-induction chemotherapy without complications. He received an allogeneic unrelated bone marrow transplant after a conditioning regimen of cyclophosphamide (Endoxan; Asta-Medica BV; Diemen, the Netherlands) therapy, total body irradiation, and low-dose antithymocyte globulin. Both donor and recipient were seronegative for cytomegalovirus. Immediately after transplantation, the patient received therapy with cyclosporine A, short-course methotrexate, and total bowel decontamination. During this time, he was nursed in a protective environment. Seven days after undergoing the bone marrow transplantation, he developed a fever. A blood culture revealed a coagulase-negative Staphylococcus infection for which he was treated with IV antibiotics (ceftazidime and teicoplanin). Six days later (13 days after the bone marrow transplantation), a chest radiograph showed bilateral pulmonary infiltrates (Fig 1).

**Physical Examination**

The results of the physical examination conducted 13 days after the bone marrow transplantation were as follows: BP, 117/52 mm Hg; pulse rate, 164 beats/min; body temperature, 39.5°C; and breathing frequency, 40 breaths/min. The jugular veins were not distended. A chest examination revealed crackles on the right ventral side, but on the left side no abnormalities were heard. Heart sounds were normal, and no murmurs were discerned. The palms of the hands showed a flaky appearance. The remainder of the physical examination revealed no abnormalities.

**Laboratory Findings**

The laboratory findings obtained 13 days after the bone marrow transplantation were as follows: total WBC count, \(<0.1 \times 10^3\) cells/µL; hemoglobin, 5.8 mmol/L; hematocrit, 26.3%; platelet count, \(7 \times 10^3\) cells/µL; prothrombin time, 17.7 s; fibrinogen, 6.5 g/L; urea, 4.2 mmol/L; creatinine, 56 mmol/L; total bilirubin, 34 µmol/L; conjugated bilirubin, 20 µmol/L; lactate dehydrogenase, 334 IU/L; γ-glutamyltransferase, 48 IU/L; alkaline phosphatase, 88 IU/L; aspartate aminotransferase, 22 IU/L; alanine aminotransferase, 10 IU/L; total protein, 40 g/L; magnesium, 0.54 mmol/L; and serum lactate, 1.8 mmol/L.

**Hospital Course**

Because the fever persisted, a fungal infection was suspected, and IV liposomal amphotericin B
(3 mg/kg/d) was added to the patient’s treatment. Next, his blood showed rapid donor myelopoietic engraftment, and his condition stabilized. Twelve days later (at 25 days after transplantation), he developed dyspnea, which rapidly progressed to complete respiratory failure for which he was mechanically ventilated with a respiratory rate of 30 breaths/min, a positive end-expiration pressure of 8 mm Hg, a maximal inspiratory pressure of 40 mm Hg, and an inspiratory oxygen fraction of 100%. His arterial blood gas levels while receiving mechanical ventilation were as follows: pH, 7.32; Po2, 68.3 mm Hg; Pco2, 64.5 mm Hg; bicarbonate, 32 mmol/L; base excess, 5 mmol/L; and oxygen saturation, 92%. The chest radiograph immediately after intubation showed bilateral diffuse airspace consolidations, with a suggestion of a cavitary lesion in the left upper lobe (Fig 2). The patient’s condition was stabilized by treatment with mechanical ventilation and the continuation of therapy with antibiotics and amphotericin B. During the next 8 days, thin-walled cavities were noted in both lungs (33 days after transplantation) [Fig 3]. A chest CT scan showed newly formed cavitary lesions with a central “ball” lesion in both lungs (Fig 4). At this time, flexible bronchoscopy demonstrated a red, diffusely swollen mucosa. BAL recovered blood. Staining and cultures for mycobacteria, Pneumocystis carinii, and other bacteria, fungi, and viruses were negative. A serum galactomannan test result was positive.

What is your diagnosis?
Figure 4. A CT scan of the chest (day 33 after transplantation) with newly formed cavitary lesions and a central ball lesion situated in an area of consolidation.
Diagnosis: Acute cavitory pulmonary aspergillosis

The spectrum of pulmonary complications after patients undergo bone marrow transplantation includes infectious and noninfectious conditions, which are classified as early or late depending on whether they occur before or after 100 days posttransplantation. In the first few weeks following bone marrow transplantation, the differential diagnosis of infiltrates includes bacterial, fungal, or viral infections, diffuse alveolar hemorrhage, and idiopathic interstitial pneumonitis. Bronchiolitis obliterans organizing pneumonia occurs after the third month following bone marrow transplantation. The patient presented in this study received a total antibiotic decontamination regimen during the transplantation period. He was already being treated IV for both viral infections (acyclovir) and bacterial infections (cefazidine/ticloplatin, later cefuroxime) when the infiltrates became visible on the chest radiographs.

Invasive pulmonary aspergillosis is a serious infection of the severely immunocompromised host due to species of Aspergillus, most commonly Aspergillus fumigatus, but also Aspergillus flavus, Aspergillus terreus, or Aspergillus niger. It is characterized by the progression of the infection across tissue planes. Vascular invasion with subsequent infarction and tissue necrosis is a hallmark. The illnesses caused by the different species of Aspergillus are clinically indistinguishable. Invasive aspergillosis can be divided into the following two distinct clinical entities: classic invasive pulmonary aspergillosis, occurring in the severely immunocompromised patient; and chronic necrotizing pulmonary aspergillosis, occurring in marginally immunosuppressed persons.

Invasive pulmonary aspergillosis generally presents as an acute, progressive infection. The major manifestation is fever that is unresponsive to broad-spectrum antibiotics and often is also unresponsive to amphotericin B therapy. Cough, chest pain, and hemoptysis also may be seen, and their presence suggests vascular invasion by the fungus. The chest radiograph findings may be normal or may reveal nodular lesions and patchy infiltrates. A CT scan may show lesions in patients with normal radiographic findings. Because of antifungal therapy and the recovery of circulating neutrophils, the infection may become better controlled with a subacute clinical course, as we believe was the case with the patient presented here. At this stage, the involved area may cavitate and localize to a smaller, more discrete area. In the literature, this condition is also called acute cavitory pulmonary aspergillosis. This condition may mimic an aspergilloma in its gross and radiologic appearance, but it differs in that the ball represents necrotic tissue that has infiltrated with the fungus, rather than a mass of Aspergillus alone. Also, the cavities are newly formed as a consequence of the fungal invasion and do not represent preexisting cavities that have become infected saprophytically.

Chronic necrotizing pulmonary aspergillosis is a form of invasive aspergillosis that is most commonly seen in patients with altered local defense from preexisting pulmonary disease or in patients with factors that mildly alter systemic immune status, such as COPD, diabetes, or alcohol abuse. The most frequent complaints are fever, cough, and sputum production.

Amphotericin B is the major antifungal drug that is used in patients with invasive aspergillosis. However, the mortality rate exceeds 50% despite aggressive antifungal therapy and ancillary measures in patients with neutropenia. Liposomal amphotericin has the advantage of administering larger doses of amphotericin B with fewer toxic effects. Itraconazole also has been proven to be useful in patients with invasive aspergillosis that is not life-threatening or that has been stabilized with amphotericin B therapy and has the advantage of being an oral preparation. In the last decade, several groups have advocated early surgical therapy in conjunction with antifungal therapy for immunocompromised patients with localized cavitary pulmonary aspergillosis. The role of surgery would be to resect the lesions, which may bleed profusely and can serve as a continued source of infection. Most data concerning the role of surgery in the treatment of patients with invasive aspergillosis are obtained from retrospective studies. Randomized data comparing surgery and antifungal treatment vs antifungal treatment alone are not available.

The diagnosis of invasive aspergillosis may be hard to establish. One of the problems in diagnosing invasive pulmonary aspergillosis is that the isolation of Aspergillus from respiratory secretions or its presence on a Gram stain preparation may be misleading, because the fungus can be a colonizing organism or the result of laboratory contamination as well. The diagnosis of invasive aspergillosis requires the demonstration of the fungus in tissue specimens. Also, Aspergillus infection should be confirmed by culture, since it cannot be diagnosed with certainty by microscopy. Other fungi such as Pseudallescheria boydii and Fusarium appear identical in histopathologic sections. This distinction is important, because these fungi are less responsive to amphotericin B therapy, which is the drug of choice for the treatment of Aspergillus infection. In the case presented, no pathogen could be identified from the sputum or BAL fluid. Culturing Aspergillus from sputum is difficult, with positive results in only 8 to 34% of
cases. BAL is an important tool in investigating pulmonary infiltrates in a bone marrow transplant recipient, with a diagnostic yield (all causes) of 50 to 75%. In patients with pulmonary aspergillosis, bronchial washings and BAL are safer, with a higher sensitivity than transbronchial biopsy. The specificity of BAL is lower than that of transbronchial biopsy but is still acceptable if the patient is considered to be at a high risk for opportunistic infections and if the organisms can be seen by staining or culture. For the diagnosis of invasive pulmonary aspergillosis, we depend largely on invasive procedures. However, immunocompromised patients often are extremely ill and have thrombocytopenia or other contraindications to biopsy. Therefore, it is mandatory to use serologic and DNA detection assays for the diagnosis of invasive aspergillosis. One currently promising noninvasive tool in diagnosing invasive aspergillosis is the serial screening for circulating galactomannan, a major aspergillar cell-wall constituent, which is released during invasive disease. Maertens et al conducted a prospective study that analyzed the diagnostic contribution and accuracy of the galactomannan test (an enzyme-linked immunosorbent assay) for diagnosing invasive aspergillosis in 191 prolonged neutropenic patients and stem cell recipients. Although serial sampling was necessary to maximize detection, they could demonstrate the presence of antigenemia in all patients with proven invasive aspergillosis. The test proved to have a sensitivity of 89.7% and a specificity of 98.1%. The positive and negative predictive values equaled 87.5% and 98.4%, respectively. Therefore, we think that the galactomannan test is useful for clinical decision making. A confirmed positive test result (especially rising titers) in a relevant clinical setting should encourage clinicians to start (or change to) antifungal therapy. However, it should be kept in mind that the species specificity of the assay cannot exclude the involvement of other fungal pathogens with a similar clinical presentation (eg, Fusarium, Alternaria, and Mucorales) and does not provide information about coinfections (eg, Cytomegalovirus and Candida). In conclusion, we believe that galactomannan detection provides supportive evidence of the Aspergillus etiology of an infectious process in the right context. It does not replace other diagnostic tools in the workup of unexplained fevers and in the exploration of invasive fungal infections in general in high-risk hematologic patients.

This case presented a patient with high-risk acute myeloid leukemia who was undergoing chemotherapy and myeloablative conditioning before bone marrow transplantation, with an occurrence of patchy bilateral pulmonary infiltrates and subsequently pulmonary cavitations due to Aspergillus infection. Albeda et al described 11 patients undergoing bone marrow transplantation for acute leukemia who developed one or more cavities within 6

**Figure 5.** Gross appearance of a cavitary lesion in the right lower lobe demonstrating the central ball lesion.
days after recovery of the bone marrow. Six of these patients died of Aspergillus infection within 2 months. We think that these cases are similar to the case of acute cavitary pulmonary aspergillosis that we have presented, occurring in the phase of granulocyte reconstitution after bone marrow transplantation. The clinical course of these patients may be transformed into a subacute form of aspergillosis by the neutrophil recovery of the bone marrow and, possibly, by promptly initiated antifungal therapy. Whether these patients will die of the Aspergillus infection or the underlying hematologic condition is hard to predict.

In our patient, screening for tuberculosis was performed prior to the bone marrow transplantation. A presentation with multiple cavitating nodules would be rare for P carinii, Cytomegalovirus, bronchiolitis obliterans-organizing pneumonia, idiopathic interstitial pneumonitis, or ARDS. However, other non-Aspergillus fungal pathogens could not be excluded (eg, Mucorales, Alternaria, and Fusarium). The chest CT scan findings and a positive result for the galactomannan test were suggestive of invasive Aspergillus infection, for which the patient was treated with IV liposomal amphotericin B. Despite this treatment, the patient’s condition deteriorated, and he died 14 days thereafter. At autopsy, the diagnosis of acute cavitary pulmonary aspergillosis was confirmed (Figs 5, 6), and A fumigatus was cultured from the lung. No sign of graft-vs-host disease was demonstrated histologically in the lungs.

**Clinical Pearls**

1. Invasive pulmonary aspergillosis should be suspected when new pulmonary infiltrates appear in the first few weeks following bone marrow transplantation.

2. Cavities may appear due to the recovery of circulating neutrophils in patients with invasive pulmonary aspergillosis.

3. The antifungal therapy of choice is high-dose IV liposomal amphotericin B in the critically ill patient. However, when the condition of the patient improves, itraconazole is a satisfactory alternative.

4. Invasive pulmonary aspergillosis with cavity formation may mimic aspergilloma radiologically.

5. The galactomannan test is a useful screening aid to the early identification of invasive aspergillosis in the immunocompromised host.

**Selected Readings**


