Aspergillus fumigatus, a Rare Cause of Fatal Coronary Artery Occlusion

**Summary:** Endocarditis by *Aspergillus* species in patients without prior cardiovascular surgery is extremely rare and difficult to diagnose. We report and discuss a 69-year-old patient with hairy cell leukemia who developed severe bilateral pneumonia and metastatic subcutaneous nodules from which *A. fumigatus* was cultured. He died after 18 days of treatment with an adequate dose (0.7 mg/kg/day) of amphotericin B intravenously. Fungal endocarditis and a myocardial infarction due to a septic thrombotic occlusion of the left coronary artery by *A. fumigatus* appeared to be the cause of death. *A. fumigatus* could still be cultured from the aortic valve postmortem despite a total dose of 756 mg amphotericin B. In case of metastatic spread of *Aspergillus* spp., endocarditis should be suspected.


**Introduction**

Endocarditis by *Aspergillus* species without prior cardiovascular surgery is extremely rare. Most patients are immunocompromised. Establishing the diagnosis is difficult because the clinical presentation is nonspecific and blood cultures are usually sterile. Embolisation to major systemic or pulmonary arteries is a characteristic complication and usually results in multiple foci of infection in lung, kidney, spleen and brain, as well as signs of vascular occlusive phenomena in these organs or in the extremities [1–4].

**Case Report**

In a 69-year-old-man, with longstanding pancytopenia, hairy cell leukemia was diagnosed on bone marrow biopsy. He was treated with alpha-interferon (dose $3 \times 10^6$E units a day s.c.). He was previously healthy, without cardiac disease. On the 12th day of treatment he was admitted with fever, dyspnoea, cough and the production of hemorrhagic sputum. A bronchopneumonia was visible in the left upper lobe on the chest X-ray. Gram stain of the sputum did not reveal a pathogenic bacterium. The patient was treated with amoxicillin and became afebrile from the next day on. Several sputum cultures showed growth of commensal flora and were negative for *Legionella pneumophila* and fungi. Serum precipitating antibodies (Ouchterlony technique) to antigens of *Aspergillus fumigatus* (metabolic antigen and somatic antigen), *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nidulans* and *Aspergillus terreus* were not found (Diagnostics Pasteur, France). Since the white cell count was $0.7 \times 10^9$/l the patient was nursed in reversed isolation and ciprofloxacin and ketoconazole were started for intestinal decontamination. The leucocyte count was normal on the 7th day and ciprofloxacin and ketoconazole were stopped, but the
pneumonia extended to the left lower lobe and on the 14th day a bronchoscopy was performed. Because of the low platelet count (36 × 10⁹/l) no biopsy was taken. The broncho-alveolar lavage did not reveal a pathogenic bacterium or fungus. Because the culture of the nose showed growth of *Staphylococcus aureus*, amoxicillin was changed to vancomycin and erythromycin was added because of the possibility of atypical pneumonia. Although the infiltrate in the left lower lobe partly resolved, the pneumonia extended to the right lung (Figure 1).

Because of the development of an allergic rash and absence of any beneficial effect, all antibiotics were stopped on the 26th day. Around the 28th day the patient developed palpable purpura on his extremities and several subcutaneous nodules on his back, with a diameter of 2 cm. Three nodules were surgically removed, and microscopic examination using fluorescence (Fungiqual, CIBA [5]) revealed septate dichotomous branching hyphae. Histological examination showed a necrotising inflammatory infiltrate (with hyphae). Cultures yielded growth of *Aspergillus fumigatus*. The diagnosis of disseminated pulmonary aspergillosis with metastatic subcutaneous abscesses was considered, and on the 36th day amphotericin B was started intravenously (0.7 mg/kg/d). Although the subcutaneous abscesses disappeared after 10 days of therapy, the patient's condition continued to deteriorate. He suddenly died on the 53rd day, despite attempts of cardiopulmonary resuscitation.

At autopsy the immediate cause of death was related to a myocardial infarction with a thrombotic occlusion of the left coronary artery. To our knowledge, this fatal complication of disseminated Aspergillus infection has not been described before. There is one report, however, describing a patient with acute occlusions of the right axillary, left iliac, left popliteal arteries and the distal aorta by embolisation from an Aspergillus valvular endocarditis [9]. If the diagnosis had been established before death, surgical valve reconstruction might have been considered, since treatment with amphotericin B alone does not lead to sterilisation of the cardiac valves [1, 4, 9]. This is demonstrated by the fact that *A. fumigatus* could still be cultured postmortem from the valvular vegetations despite a total dose of 756 mg of amphotericin B. There is no general agreement on optimal dosage schedules for amphotericin B. This concerns the optimal daily doses as well as the total dose. We think that it is seldom necessary to use more than 0.5 mg/kg/day and consider 0.7 mg/kg/day a high dose [10]. The addition of rifampicin or flucytosin to amphotericin B for Aspergillus infections remains controversial [2, 9].

This case report also demonstrates the difficulties in diagnosing pulmonary aspergillosis [2, 4]. Fungal cultures of sputum and bronchoalveolar lavage were negative, but a lung biopsy could not be performed. The negative serologic tests are probably associated with the immunocompromised state of the patient. We believe that diagnosing invasive aspergillosis needs invasive procedures such as lung biopsy or, as in our patient, surgical removal of infected tissue.

**Discussion**

We report an immunocompromised patient who developed pulmonary aspergillosis, fungal endocarditis with myocardial and pericardial invasion and septic embolisation by *A. fumigatus*. The diagnosis of disseminated aspergillosis was established before death by culturing *A. fumigatus* from the metastatic subcutaneous nodules.

We did not consider the diagnosis endocarditis because of the complete absence of cardiac symptoms and pathologic murmurs, but the subcutaneous nodules could have been a clue to the diagnosis. Aspergillus endocarditis is associated with embolic phenomena more commonly than bacterial endocarditis. Organs most frequently involved are brain, kidney, spleen and lungs [1–4, 6]. Metastatic skin involvement occurs very rarely as a consequence of disseminated aspergillosis. We could only find three reports on disseminated endocarditis by aspergillosis with cutaneous lesions which were located on the lower part of the trunk and the extremities [6–8]. All three patients were immunocompromised by severe underlying diseases or immunosuppressive therapy. Of these patients, one had a mural endocarditis with emboly to the central nervous system and the skin [6]. He did not survive despite systemic antifungal therapy and surgical intervention.

Our patient died from a myocardial infarction due to fungal occlusion of a coronary artery. To our knowledge, this fatal complication of disseminated Aspergillus infection has not been described before. There is one report, however, describing a patient with acute occlusions of the right axillary, left iliac, left popliteal arteries and the distal aorta by embolisation from an Aspergillus valvular endocarditis [9]. If the diagnosis had been established before death, surgical valve reconstruction might have been considered, since treatment with amphotericin B alone does not lead to sterilisation of the cardiac valves [1, 4, 9]. This is demonstrated by the fact that *A. fumigatus* could still be cultured postmortem from the valvular vegetations despite a total dose of 756 mg of amphotericin B. There is no general agreement on optimal dosage schedules for amphotericin B. This concerns the optimal daily doses as well as the total dose. We think that it is seldom necessary to use more than 0.5 mg/kg/day and consider 0.7 mg/kg/day a high dose [10]. The addition of rifampicin or flucytosin to amphotericin B for Aspergillus infections remains controversial [2, 9].

**References**


NOTICE

The German Institute for Standardization (Deutsches Institut für Normung e. V. [DIN]) has released the following results of the Working Advisory Committee E 10, “Chemotherapeutic Investigation Methods”:

1. For the series of standards DIN 58 940, “Methods for Testing Sensitivity of Bacterial Pathogens (except mycobacteria) to Chemotherapeutic Agents” (October 1991):

   **Ampicillin:** The zone of inhibition for the classification “sensitive” has been changed from 19 to 22 mm.

2. Changes:
   a. Cefotiam: Because of the higher daily dosage of 3 × 1 g (instead of the previous 2 × 1 g) approved by the German Health Office (Bundesgesundheitsamt [BGA]), the lowest breakpoint value has been increased from 0.5 mg/l to 1.0 mg/l.
   b. Vancomycin: The MIC value for “intermediate” (moderately sensitive) has been established as > 4 to 8 mg/l. Accordingly, the MIC value for the classification level “resistant” (insensitive) has been changed to > 8 mg/l.
   c. The MIC breakpoint value of ≥ 0.1 mg/l for potential β-lactamase-producing staphylococci has been changed to ≥ 0.125 mg/l in accordance with the dilution steps, since otherwise calculation of collectives results in serious errors.

3. **Newly approved: Cefuroxime Axetil:**
   - Dosage = 2 × 250 mg/d
   - MIC Breakpoint Values:
     - Sensitive = ≤ 1 mg/l
     - Intermediate = 2–4 mg/l
     - Resistant = ≥ 8 mg/l

Information on standardization work can be obtained from:
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