

Invasive aspergillosis after bilateral lung transplantation in cystic fibrosis

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Introduction

Cystic fibrosis (CF) is an inherited disease. Although, in general a multiorgan disease, the respiratory disorders cause considerable morbidity and nearly all of the mortality in patients with CF. Recently, lung transplantation became a viable option for those CF patients with end-stage lung disease and short life-expectancy (1,2).

Case Report

A 30-year-old male with CF was accepted for bilateral lung transplantation at St. Antonius Hospital, Nieuwegein, The Netherlands. Previously, he had a complicated pneumothorax on both sides, gastrointestinal problems, diabetes mellitus, pulmonary infections, and colonization with *Aspergillus fumigatus* without evidence of allergic bronchopulmonary aspergillosis. Post-operative, several complications occurred: three periods of rejection, an inappropriate reaction to immunosuppressive, infections (by several *Pseudomonas* species and cytomegalo-virus), nutritional and neurological problems. However, the major complication was a disseminated infection with *A. fumigatus* located in the skin, brains, ears and lungs. This diagnosis was established by specimen cultures, serological methods to detect antibodies to *A. fumigatus* (precipitins, RAST and immunoblot-patterns in time). Antibiotic treatment was performed by tobramycin, ceftazidime, ciprofloxacin, aciclovir, ganciclovir, as well as empiric treatment by amphotericin B ($0.5 \text{ mg kg}^{-1} \text{ day}^{-1}$) and flucytosine. Immunosuppression therapy included cyclosporine, azathioprine, methyl-

prednisolon, anti-human thymocytes globulin and anti-human lymphocytes immune globulin.

Sixty-two days post-operative, the first clinical demonstration of invasive aspergillus (i.e. epilepsy), became manifest in this patient. Three months after transplantation, the patient died due to haemoptoe.

Pathological Findings

Post-mortem examination demonstrated signs of bronchitis, bronchiolitis obliterans, pulmonary aspergillosis and Adult Respiratory Distress Syndrome. A fistula between the bronchus of the right middle lobe and the pulmonary artery due to an invasive aspergillosis was the cause of the lethal bleeding (Plate 1). In addition, an invasive aspergillo-sis infection of the brain was demonstrated by a local lesion in the right occipital lobe, with involvement of the vessels with a diameter of 2.5 cm.

Discussion

A change towards more aggressive treatment in CF patients has lengthened their life-expectancy and many patients survive into adolescence. In accordance, lung transplantation has become one of the tools in the therapeutic regimen. However, shortage of suitable donor organs requires careful selection of recipients who would benefit from transplantation. Therefore, individual prognosis, quality of life and degree of disability must be evaluated both for surgical and post-operative management (1,2). Invasive disseminated aspergillosis is one of the most devastating opportunistic infections, which usually occurs in immunocompromised patients (3). Furthermore, diabetes mellitus – which occurs in about 15% of CF patients – predisposes to many infections. Aspergillus infections occur in 2–8% of patients with solid organ transplants (4). However, in lung transplantation patients, aspergillosis is often under-diagnosed since

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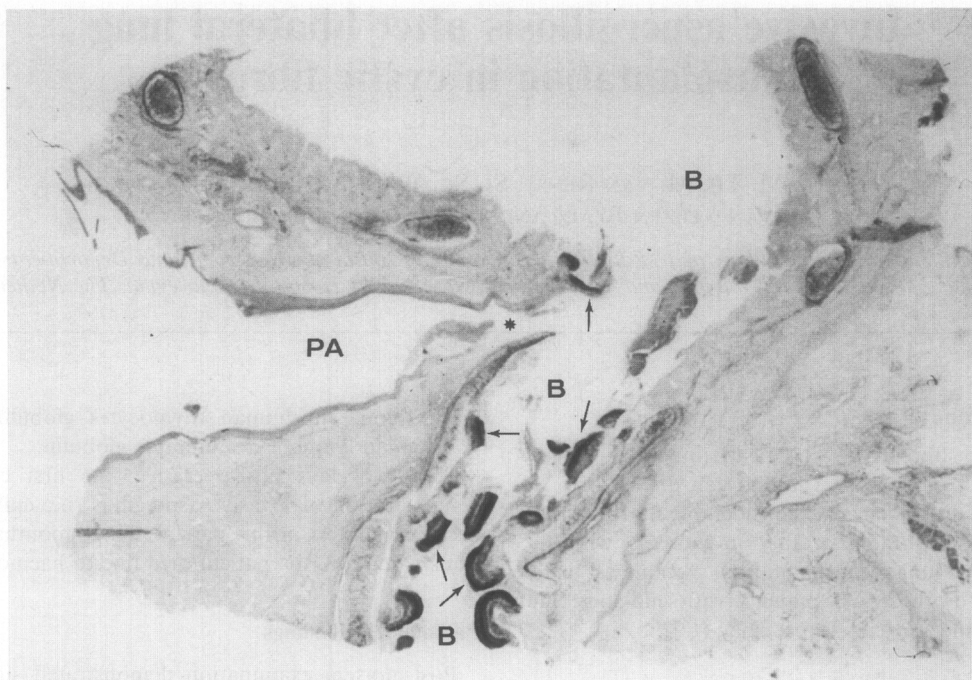


Plate 1 Bronchial structure (B) and adjacent pulmonary artery (PA). Accumulation of *A. fumigatus* on the bronchial mucosal surface and invasion of the bronchial wall causing a fistula (*) between the bronchus of the right middle lobe and pulmonary artery.

the underlying disease itself may be associated with similar symptoms (4,5). For those with disseminated disease and invasion of the central nervous system, outcome has mostly been fatal (4–7). Cerebral invasion by haematogenous dissemination may result in a variety of neurological signs. Cerebral aspergillosis should be strongly suspected in patients who develop pulmonary infiltrates and focal neurological signs, especially if they have received high dose steroids (6,7). Boon *et al.* (6) found invasive cerebral aspergillosis in 20% ($n=9$) of the patients who died after liver transplantation. In only two of these cases, the diagnosis was established before death. A biopsy specimen of an unusual rash may be the only means of establishing an early diagnosis of a disseminated fungal infection and is worthy of consideration. Therefore, the dermatological manifestations of systemic aspergillosis should not be overlooked.

The case described above illustrates a disseminated manifestation of infection with *A. fumigatus* after bilateral lung transplantation. Predisposing factors — such as prolonged survival through intensive supportive treatment, rejection episodes with, as a consequence, an increase of immunosuppression, which predispose for infections, diabetes mellitus, and high dose corticosteroids — may have given the

organism an opportunity to disseminate more widely (2,8). Before transplantation, colonization with *A. fumigatus* in the lung alone was documented in this patient. Seven days after transplantation, cultures of wound, cerumen and drains, as well, became positive for *A. fumigatus*. Therefore, we suggest that colonization before operation predisposes for invasive aspergillosis and treatment should be considered.

Despite antifungal treatment, the CF patient described died due to invasion of *A. fumigatus*. With regard to aspergillosis, the prognosis of survival after lung transplantation in CF depends on (pre-operative) clinical presentation and pre-operative screening (using well-defined criteria) for colonization of the entire respiratory tract, with high attention for the diverse manifestations of disseminated aspergillosis.

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