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ORIGINAL ARTICLE

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aspergillosis after lung transplantation

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Abstract Aspergillus infections in lung transplant patients are frequently reported with a large pattern of manifestations varying from simple colonization of the lungs to complicated infections. Pulmonary invasive aspergillosis and disseminated aspergillosis often result in death. The majority of cases occur during the first months after transplantation with pulmonary involvement and have been described as the first clinical localization of the disease. Here we present the first reported case of an endophthalmitis caused by Aspergillus fumigatus developing 18 months after lung transplantation, and presenting as a manifestation of invasive aspergillosis.

Key words Invasive aspergillosis · Lung transplantation · Aspergillus endophthalmitis · Antifungal therapy · Antifungal prophylaxis

Abbreviations *IA* Invasive aspergillosis · *EAE* Endogenous aspergillus endophthalmitis · *BAL* Bronchoalveolar lavage

Invasive aspergillosis (IA) is a serious complication of immunosuppressive treatment occuring in about 15% of all heart-lung transplant recipients [5, 7] generally during the first 3–6 months following solid-organ transplantation [6, 14]. IA carries a high mortality rate due to the difficulty in establishing an early diagnosis and to the problematic management of certain anti-fungal drugs. The portal of entry for the Aspergillus is usually the respiratory tract, and from the lung it may disseminate to almost any organ including the brain, liver, spleen, heart, pericardium and gastrointestinal tract. Endogenous Aspergillus endophthalmitis (EAE) is rare. This report describes a case of endophthalmitis as the first clinical manifestation of disseminated aspergillosis observed late after a single lung transplant recipient.

A 48-year-old male underwent left single lung transplantation for idiopathic pulmonary fibrosis. Post transplant immunosuppression consisted of cyclosporine (to maintain whole blood levels of 400–450 ng/ml in the first month and then 250–300 ng/ml), azathioprine (1.5 mg/kg per day) and prednisone at 0.5 mg/kg per day, tapering to 0.25 mg/kg per day over the first 6–9 months, then to 15 mg every other day after one year. A 5-day course of anti-thymocyte globulins was administered in the immediate postoperative period. Four weeks post-transplant, cytomegalovirus (CMV) viremia was documented, and the patient received CMV pre-emptive therapy with ganciclovir for 14 days. Nevertheless a histopathologically documented CMV pneumonia developed, and a 21-day course of foscarnet therapy was initiated with a gradual resolution of symptoms and negativity of the tissue biopsy. Within 5 months after surgery, the patient experienced two episodes of rejection, both successfully treated with three pulses of methylprednisolone.

Seventeen months after transplantation, during a follow-up examination, a routine bronchoscopy with transbronchial biopsy and

bronchoalveolar lavage (BAL) was performed. There were no evidence of rejection or tracheobronchial disease; however two colonies of Aspergillus fumigatus were cultured from BAL. No clinical symptoms or abnormality in laboratory data were present, and the chest X-ray was normal. Itraconazole treatment (400 mg/day for 4 weeks, then 200 mg/day) was started and the patient discharged.

Three weeks later, the patient was admitted to our ward with a 3-day history of fever, frontal headache and a sudden blurred vision of his left eye. On physical examination, his overall appearance was quite good. Medication on admission included cyclosporine 120 mg twice a day, azathioprine 100 mg daily, and prednisone 15 mg every other day. His temperature was 38 °C, blood pressure 140/100 mmHg, respirations 22/min, and heart rate 90 beats/min. Cardiopulmonary auscultation was normal, and only a mild injection of the left conjunctiva was disclosed. Laboratory tests showed the following values: white blood cell count, 7.9×10^9/l, with 90% neutrophils, 3% lymphocytes, and 5% monocytes; hemoglobin, 95 g/l; platelets, 300×10^9/l; creatinine, 135 μmol/l (normal range, 62–115 μmol/l); urea, 14 mmol/l (normal range, 2.5–7.5 mmol/l); total bilirubin, 11.6 μmol/l (normal range 1.7–17.0 μmol/l); C-reactive protein, 7 mg/dl (normal range, 0–10 mg/dl). CMV antigen assay (pp65 protein) was positive (550/200,000 white blood cells). Cultures from blood and BAL showed no pathogens and both brain and thorax computed tomography (CT) scannings were normal. Bedside ocular examination revealed persistent blurred vision; the fundus in the left eye showed yellow fluffy chorioretinal infiltrates associated with retinal hemorrhages in the posterior area (Fig. 1).

In view of the immunosuppressed condition together with the high level of CMV antigenemia, the ocular findings were attributed to a CMV retinitis and ganciclovir therapy was reinstated intravenously. Regardless of antiviral treatment, within two days, more severe visual loss, pain, photophobia, redness, and conjunctival chemosis rapidly developed in the involved eye. A further ophthalmologic examination disclosed an important vitritis with massive retinal white infiltration of posterior and temporal retinal quadrant. A clinical diagnosis of fungus endophthalmitis was made, and subsequently a vitreous needle aspirate confirmed the growth of Aspergillus fumigatus. A vitrectomy was performed and intravitreous amphotericin B injections and systemic liposomal amphotericin B (5 mg/kg per day) were started. Baseline immunosuppression remained unchanged during the entire process.

After 15 days of systemic and local antifungal therapy, a hemorrhagic abscess developed in the anterior segment of the left eye (Fig. 2), and the possibility of enucleation was raised. Eye surgery was deferred due to patient's refusal. Seven days later, after a dosage reduction of liposomal amphotericin B due to the deterioration in renal function (creatinine level was 292 μmol/l), an endophtalmitis of the right eye developed, and multiple skin nodules on the trunk and arms presented. A biopsy of one of the lesions revealed Aspergillus fumigatus histopathologically and in culture. A surgical excision of all the nodules was performed (Fig. 3). Furthermore, at the same time, the clinical conditions of the patient deteriorated with the presence of fever, cough, and polypnea. A sputum culture was positive for A. fumigatus, and a repeated chest X-ray showed an ill-defined infiltrate at the upper right lobe. A CT scan confirmed the presence of a single, thick-walled abscess, and a surgical excision of the right lung was performed. At biopsy of the native lung, extensive necrosis with invasive aspergillosis was found. Despite maximal support therapy, the patient's condition deteriorated further. The patient died 15 days after native lung excision. Autopsy findings confirmed a disseminated aspergillosis with ocular, pulmonary and skin manifestations.

Discussion

Invasive aspergillosis remains one of the major challenging opportunistic complications in lung transplantation and is associated with a mortality of nearly 100% [3]. Lung transplant recipients are particularly at risk for this mold infection since Aspergillus is ubiquitous in the environment, has easy access to the airways by direct inhalation, and is difficult to treat efficaciously. In addition, in single lung transplantation Aspergillus often colonizes the native, structurally damaged lung that may become a potential source of infection [13].

From the lungs, Aspergillus spp may disseminate to almost any organs with a predilection for the central nervous system. Among unusual presentations of aspergillal infections, endophthalmitis may occur. In general it has been reported in intravenous drug abusers, but immunocompromised patients with leukemia, bone marrow, or solid organ transplantation are also at particular risk [12].

In our report, EAE occurred 18 months after transplantation, as a first clinical manifestation of disseminated aspergillosis, in the absence of other localizing systemic symptoms. It was a late infectious complication of lung transplantation even if Aspergillus infections usually occur in the first three-six months after surgery [9], when immunosuppression is maximal. Indeed, our patient was profoundly immunosuppressed due to the duration of the immunosuppressive regimen and to the recurrent CMV disease. Some authors note a high incidence of fatal fungal infections in patients treated for multiple rejection episodes or in those receiving large doses of corticosteroids [2, 8]. Furthermore, it has been reported that CMV enhances the risk of bacterial and fungal infections, increasing the mortality rates [11, 14].

There are two other previous reports of lung transplant recipients who presented an Aspergillus endophthalmitis: in both cases it developed during amphotericin B (Ampho B) therapy for invasive aspergillosis and had only a post-mortem histological diagnosis [1, 4]. In this report we highlight the case of an EAE occurring as the first evidence of an invasive Aspergillus infection in a single lung transplant-recipient. It was recognized early and promptly treated without a positive response. It is likely that in our patient the drastic reduction of systemic Ampho B dosage regimen, due to renal impairment, helped in determining the rapid onset of a subsequent fatal disseminated aspergillosis.

One might speculate that itraconazole prophylaxis, administrated to our patient, was unsuccessful in eradicating the fungus prior to invasion and had even delayed a pulmonary fungal infection diagnosis. The role of antifungal prophylaxis in eradicating Aspergillus colonization has still to be defined. The use of Ampho B is problematic for its toxic effects, particularly nephrotoxicity, and prospective data on the use of itraconazole are still

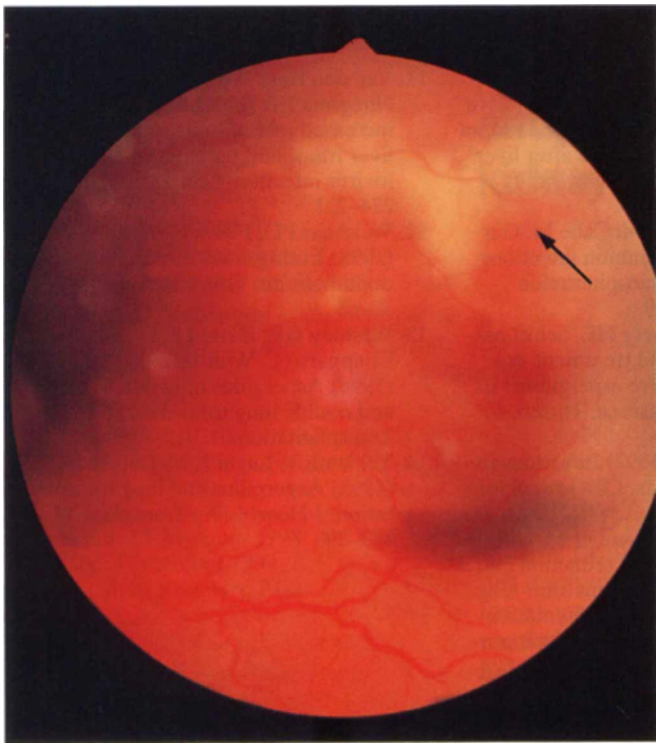

Fig. 1 Yellow fluffy chorioretinal infiltrates (*arrow*) associated with retinal hemorrhages in the posterior area of the left eye

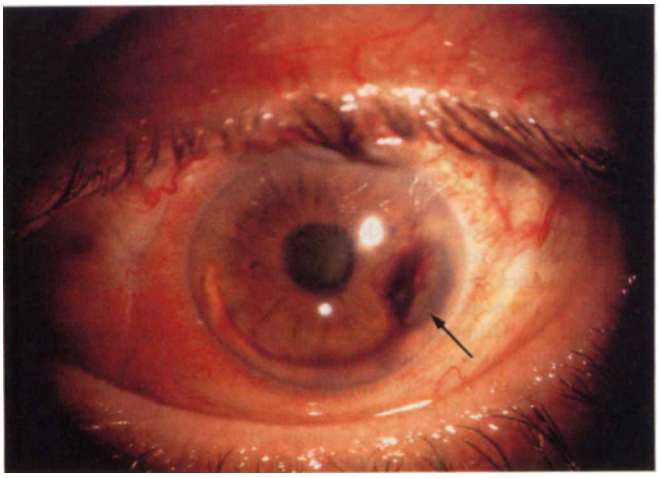

Fig. 2 Hemorrhagic abscess (arrow) in the anterior segment of the left eye

not available. The experience with inhaled Ampho B is also limited, even though a significant reduction in fungal infections in patients receiving a primary post-transplant aerosolized Ampho B prophylaxis [10] has recently been demonstrated.

We therefore suggest that an early and aggressive anti-fungal prophylaxis should be considered to prevent the dissemination of the disease even in the presence of few colonies of aspergillus, although the delineation between infection and colonization is difficult, and the time of invasive aspergillus diagnosis often leaves little possibility of treatment, especially for patients with single-lung transplantation, where the native lung may represent an important source of the infection. In this view, an early surgical intervention both of the native lung and of the metastatic focus could be encouraged in selected cases. These measures, along with more active and safer anti-fungal agents, need to be investigated in further studies.

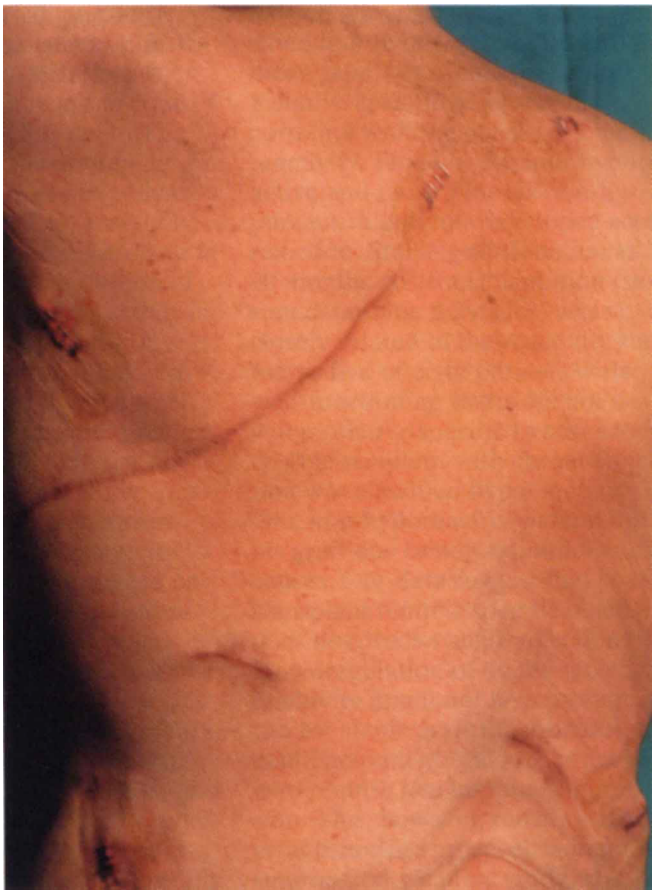

Fig. 3 Multiple Aspergillus nodular lesions on the patient's trunk: sites of surgical excision

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