LETTER TO THE EDITOR

Radiological resolution of cavitating *Aspergillus fumigatus* infection following treatment with oral voriconazole in two lung transplant recipients

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Invasive aspergillosis is the most common invasive mould infection worldwide [1]. Fungal infections with *Aspergillus* species are a particular threat to lung transplant recipients because the transplanted organ is continuously exposed to these ubiquitous pathogens. In the transplanted lung, *Aspergillus* can simply colonize the airway, cause tracheobronchitis or invasive pulmonary aspergillosis (IPA). In one case series these complications occurred in 26%, 4% and 5% of lung transplant recipients respectively. Although IPA infections are infrequent, they can be rapidly progressive and often fatal with a mortality rate of 73% [2]. Diagnosis is difficult and in order to standardize comparisons of response to treatment, disease is defined according to European Organisation for Research and Treatment of Cancer (EORTC) guidelines [3]. The response to treatment is often poor and the optimal duration of treatment is uncertain. We present two cases of cavitatory lung disease secondary to *A. fumigatus* infection in ambulatory lung transplant recipients. The condition responded to outpatient treatment with oral voriconazole over a 6–9-month period. The duration of treatment was decided based on outpatient radiological surveillance of the lung disease. We then discuss the drugs currently available in the management of IPA.

The first case is a 51-year-old lady who had undergone bilateral sequential single lung transplantation in January 1997 for bronchiectasis because of recurrent childhood respiratory infections (which infections is unknown). The patient remained in good health for 4 years. In September 2001, she suffered an episode of grade A2 acute rejection that was treated with 1 g methylprednisolone once daily for 3 days followed by a reducing dose of oral prednisolone. Her cyclosporin maintenance levels were increased in an attempt to prevent further episodes of rejection. Three months later, the patient was admitted to hospital with increasing exertional dyspnoea and a severe deterioration in her spirometry. At bronchoscopy, the appearance of the airways was consistent with tracheobronchitis, and large volumes of creamy secretions were present. A chest radiograph showed a cavitating lesion in the right upper lobe. High resolution computerized tomography (HRCT) thorax (Fig. 1a) showed at least three cavitating lesions, two in the right upper lobe and one in the left upper lobe with areas of soft tissue within the cavities. *Aspergillus fumigatus* was isolated from sputum. Treatment with voriconazole 200 mg orally twice daily was commenced. As the patient felt well and was ambulatory she was discharged on treatment with continuing oral voriconazole. The patient had regular 8-weekly follow-up HRCTs that demonstrated progressive improvement in the size of the cavities. After 9 months of treatment with oral voriconazole, HRCT (Fig. 1b) demonstrated diminution of the fungal cavities towards nodular scars and the treatment with oral voriconazole was stopped.

The second case is a 25-year-old man who underwent heart–lung transplantation for cystic fibrosis (CF) in early 1999. He was not colonized with *Aspergillus* prior to surgery. Postoperatively he developed early cyclosporin neurotoxicity and was thus switched to tacrolimus. 30 months post-transplantation, the patient was investigated due to worsening spirometry and a diagnosis of Bronchiolitis Obliterans was made. He underwent total lymphoid irradiation for chronic rejection and 36 months post-transplantation he underwent plasmaphoresis and 4 weeks of Rituximab therapy as the presence of class II human lymphocyte antigen (HLA) donor-specific antibody was demonstrated. The deterioration in the patient's lung function subsequently stabilized. 48 months post-transplantation the patient was admitted from outpatient clinic as his chest radiograph showed new cavitating lesions in both lung fields. Clinically the patient felt well and his respiratory function was stable. HRCT (Fig. 1c) showed multiple cavities scattered around both upper lobes, the apical segment of the left lower lobe, and the lateral and medial segments of the right lower lobe. Transbronchial biopsies showed chronic Bronchiolitis Obliterans and Broncheo-alveolar lavage subsequently grew *Aspergillus* species. The patient was started on oral voriconazole and discharged from hospital. The patient was followed up regularly. HRCT (Fig. 1d) 5 months post-diagnosis of IPA shows marked resolution of the cavities and the pericavity fungal granulomas in both

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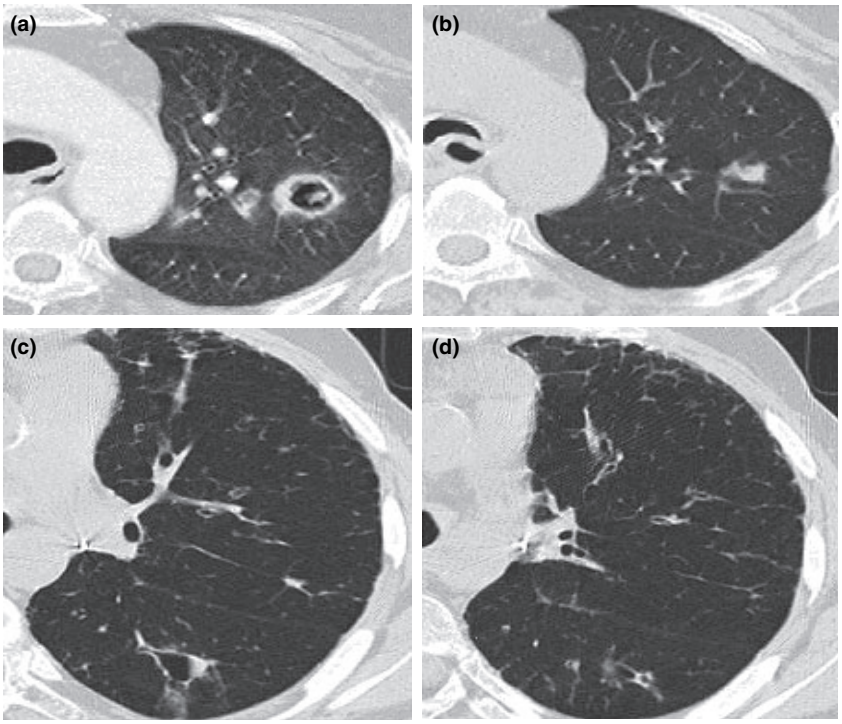

Figure 1 HRCT at diagnosis of invasive pulmonary aspergillosis (IPA; a and c) showing cavitating lesion, and corresponding HRCT images 5 months into oral voriconazole treatment (b and d). (a and b) First case; (c and d) second case.

lungs when compared with previous scans. Treatment was stopped 6 months after initiation of voriconazole therapy based to radiological resolution of the lung disease.

These cases show successful treatment of cavitatory pulmonary aspergillosis in immunosuppressed lung transplant recipients using oral voriconazole. The patients did not suffer any noticeable adverse effects. There were no disturbances in parameters of liver or renal function.

Until recently, amphotericin B has been the first-line therapy for IPA. However, it is associated with poor treatment response and survival rates of 34% overall [1]. Intolerance of amphotericin B can lead to interruption and discontinuation of therapy [4]. Lipid formulations are associated with improved tolerability but survival rates remain <65% at best [5]. Itraconazole has been primarily a second-line agent because of unreliable oral absorption.

Voriconazole has demonstrated similar efficacy compared with amphotericin as empirical antifungal therapy, first-line treatment of IPA [6] and as salvage therapy including in lung transplant recipients [7]. In the treatment of IPA, voriconazole has been associated with fewer overall adverse drug reactions when compared with amphotericin B [6]. However, some specific adverse effects were observed more frequently in patients treated with voriconazole. These included skin reactions and visual disturbance. These visual effects were transient and resolved without intervention. Infusion-related adverse events and nephrotoxic effects are common in patients receiving amphotericin B but were not observed in patients receiving voriconazole [6].

Caspofungin has demonstrated efficacy as salvage therapy in the treatment of IPA in patients refractory to or intolerant of conventional antifungal therapy [8,9] and comparable efficacy and improved tolerability when given as empirical antifungal therapy in patients with persistent fever and neutropenia [10]. Voriconazole has the advantage of an oral formulation that is well absorbed with significant cost advantages over other intravenous drug preparations. Furthermore, as in these cases, the patients can be treated as outpatients for prolonged periods while monitoring the radiological response to treatment.

Shlobin *et al.* [11] reported a case of a 7 cm mediastinal mass invading the left atrium caused by *A. fumigatus* in a lung transplant recipient. Surgical resection of the mass followed by 2 weeks of caspofungin and long-term voriconazole resulted in complete clinical and radiological resolution. However, fatal relapse occurred more than 15 months later despite continued long-term maintenance therapy with voriconazole. This case highlights the need for regular radiological and clinical monitoring of our two cases as relapse of IPA has been shown to take place several months after radiological

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resolution and despite long-term maintenance voriconazole treatment.

There now exists a choice of efficacious antifungal agents against *Aspergillus*. The choice of agent is tailored according to the clinical circumstances, the side effect profile of the drugs, drug–drug interactions and cost. The optimal duration of treatment for fungal disease in immunosuppressed patients is uncertain. In these two cases, oral voriconazole provided an effective, convenient and well-tolerated treatment for cavitiating pulmonary aspergillosis.

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