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IMPACT OF MOULD INFECTIONS IN EXPLANTED LUNGS ON OUTCOMES OF LUNG TRANSPLANTATION

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Abstract

Introduction—Little is known about the incidence or significance of mould infections in the explanted lungs of lung transplant recipients.

Method—We reviewed the histopathology of the explanted lungs from 304 patients who underwent lung transplantation at our institution from 2005–07 and received alemtuzumab induction therapy and post-transplant voriconazole prophylaxis.

Results—Invasive mould infections were present in the explanted lungs of 5% (14/304) of patients, including chronic necrotizing pneumonias ($n=7$), mycetomas (4) and invasive fungal pneumonias (3). Only 21% (3/14) received immunosuppressive therapy within one year prior to lung transplantation, suggesting that lung damage itself predisposed patients to mould infections. The risk of mould infection was higher in patients with cystic fibrosis (11%, 4/35) than other underlying lung diseases (4%, 10/269). Pulmonary mould infections were not diagnosed or suspected in 57% (8/14) of patients. Despite secondary voriconazole prophylaxis, fungal infections developed in 43% (6/14) of patients with mould infections of the explanted lungs, compared to 14% (42/290) of patients without mould infections ($p=0.01$). Three patients developed invasive fungal infections while on voriconazole prophylaxis, and three developed fungal infections more than 8 months after the discontinuation of voriconazole. The mortality attributable to invasive fungal infections among patients with mould infections of the explanted lungs was 29% (4/14).

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Titles: 1–3,5,12 had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data. They drafted the submitted article and revised it critically for intellectual content. ⁴ reviewed and interpreted the histopathological findings. ⁷ reviewed and analyzed the data, as well as assisted in the statistical analysis. ^{6,8–11} made substantial contributions to the manuscript by assisting with acquisition of data, critically reviewing and providing substantial contributions to the manuscript. All authors provided final approval of the version to be published.

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Conclusion—Invasive mould infections in the explanted lungs are often not recognized prior to lung transplantation and are associated with poor outcomes.

Keywords

Fungal infections; explanted lungs; lung transplantation

Introduction

Lung transplantation is now considered an acceptable therapeutic intervention for selected patients with end-stage lung disease. The use of aggressive immunosuppression to prevent allograft rejection leads to an increased frequency of invasive fungal infections, which are major causes of mortality in lung transplant recipients. Colonization with fungi in the lungs is considered a relative contraindication to lung transplantation (1). To our knowledge, however, there is only one study of outcomes among lung transplant recipients with evidence of fungal infections in their explanted lungs. In this report, pre-transplant pulmonary mycetomas were predictive of poor post-transplant outcome and death (2). To date, there are no studies of other types of fungal infections in lungs explanted from patients undergoing lung transplantation. The goals of this study were to evaluate the incidence of fungal infections in the explanted lungs of patients undergoing lung transplantation, and assess post-transplant outcomes.

Materials and Methods

Patients

Patients undergoing lung transplantation at the University of Pittsburgh Medical Center (UPMC) between January 2005 and December 2007 were enrolled. The standard UPMC practice is to closely inspect the donor and recipient's bronchi, and the recipient's chest and pleural cavity at the time of transplantation, and to routinely collect swabs for bacterial cultures. Fungal cultures are not performed routinely, but rather at the clinical discretion of the surgeons. The recipient's explanted lungs are sent to the pathology where digital images of the lungs are captured and the gross appearance described in detail. On a routine basis, the bronchial and vascular resection margins, hilar lymph nodes, and representative sections of each lobe of the lungs are sampled and submitted for histopathologic evaluation. Additional tissue samples are taken if there are lesions that are suspicious for infections, tumors, or findings suggestive of processes other than the underlying end-stage lung disease. All pathology information is included in the patients' electronic records.

The pathology reports of the explanted lungs from all patients were reviewed for evidence of fungal infections caused by moulds. The patients' medical records and imaging studies were reviewed. The outcomes of patients with fungal infections in the explanted lungs were compared with those of all patients who underwent lung transplantation during this period of time.

Standard immunosuppression included alemtuzumab induction therapy, followed by tacrolimus, mycophenolate, and prednisone (5 mg/day). Standard antimicrobial prophylaxis included oral voriconazole, valganciclovir and trimethoprim/ sulfamethoxazole.

This study was reviewed by the Institutional Review Board at UPMC and classified as exempt due to its retrospective and de-identified nature.

Definitions

Mould infections of the explanted lungs were defined as the presence of fungal elements suggestive of mould organisms in the explanted lung. Mould infections were further defined

as *mycetoma* (fungus ball with hyphal elements seen within the cavities but without evidence of tissue invasion), *invasive fungal pneumonia* (tissues with histological evidence of pneumonia and invasive hyphal elements), and *chronic necrotizing fungal pneumonia* (hyphal elements associated with necrotizing granulomatous pneumonia or bronchitis/bronchiolitis) (3).

Post-transplant invasive fungal infections due to either yeasts or moulds were classified as “proven” or “probable” by EORTC/MSG criteria(4). Post-transplant invasive fungal infections were further categorized as endobronchial, pulmonary, extra-pulmonary and disseminated.

Statistical analysis

Comparison of dichotomous variables was made using chi-square or Fisher’s exact test. Continuous variables were reported as median $\pm$ standard deviation and the difference between groups was calculated using Mann-Whitney U test. Survival times free of fungal infection were calculated from the date of transplantation to the date of fungal infection diagnosis. P-values ≤ 0.05 were considered significant.

Results

Demographics

Between January 2005 and December 2007, 316 patients underwent lung transplantation at UPMC [Table 1]. Alemtuzumab induction and post-transplant voriconazole prophylaxis are standard among our lung transplant recipients. Ten patients who did not receive one or both of these therapies, and two patients in whom long-term follow-up were not available were excluded. None of the 12 excluded patients had mould infections in their explanted lungs. The study was comprised of the remaining 304 patients.

Fungal infections caused by moulds in the explanted lungs

Fungal infections due to moulds were found in the explanted lungs of 5% (14/304) of patients [Table 2]. Three distinct types of fungal infection were evident: mycetoma (29%, 4/14), chronic necrotizing pneumonia (50%, 7/14), and invasive fungal pneumonia (21%, 3/14); focal pulmonary abscesses were also visualized in all three cases of invasive fungal pneumonia. All except one patient with mould infections of the explanted lungs underwent double lung transplantation.

The most common underlying diseases were COPD (29%, 4/14) and cystic fibrosis (29%, 4/14). The risk of having mould infection in the explanted lung was higher in patients with cystic fibrosis (11%, 4/35) than in those with other lung diseases (4%, 10/269; $p=0.06$).

Pre-transplant diagnosis and treatment

A pre-transplant diagnosis of pulmonary fungal infection was made or suspected in 43% (6/14) of patients [Table 2]. In two patients (patients 1 and 2), aspergillomas were diagnosed based on the computed axial tomography (CT) scan of the chest and positive sputum cultures. In two other patients (patients 5 and 6), fungal infections were diagnosed by CT scans showing pulmonary nodules or cavities, cytology or culture. In two patients with cystic fibrosis, fungal infections were suspected based on multiple sputum cultures growing *Aspergillus* and *Scedosporium* (patients 7 and 12, respectively). Their pre-transplant CT scans (performed 3 and 16 months before transplant) did not show any radiological findings suggestive of pulmonary infection. These 6 patients were treated with antifungal agents for a median of 4 months before lung transplantation [Table 2].

Fungal infections were not suspected prior to lung transplantation in 57% (8/14) of patients. All 8 patients with unsuspected infections had chest radiographs and CT scans within 1 year prior to transplantation (median: 4 and 6 months, respectively). Moreover, 3 patients had chest CT scans within 2 months, and 3 had chest radiographs within 1 month of transplant. None of the imaging studies revealed changes compared to previous studies, nor were findings suggestive of fungal infections. Cultures of respiratory samples were obtained in only 25% (2/8) of these patients; neither yielded a fungal organism.

During lung transplant, surgeons ordered fungal cultures from bronchial swabs of the native lungs in 71% (10/14) of patients. Only 40% (4/10) of these patients had cultures that revealed a fungus. Lung tissue was not sent for fungal culture in any patients.

Post-transplant outcomes

All patients with fungal infections in their explanted lungs received secondary voriconazole prophylaxis after transplant for a median duration of 10 months. Post-transplant invasive fungal infections developed in 43% (6/14) of patients with mould infections in the explanted lungs, compared to 14% (42/290) of patients without such infections ($p=0.001$). Cox proportional analysis showed a higher risk of fungal infection (hazard ratio, 4.0, 95% CI, 1.7–9.4) in patients with pre-transplant mould infection.

Three patients developed breakthrough post-transplant invasive fungal infections while receiving voriconazole secondary prophylaxis. One patient (patient 12) had suspected fungal pneumonia due to *Scedosporium inflatum*, and was treated with antifungals for 5 months before transplantation. She developed a dissecting ascending aortic pseudoaneurysm, mediastinitis and brain abscess due to *S. inflatum* seventeen weeks after transplantation. A second patient (patient 10) with necrotizing fungal pneumonia in the explanted lung developed invasive endobronchial mould infection at the anastomotic site two weeks after transplantation. A third patient (patient 3) with mycetoma in the explanted lung allograft developed invasive candidal endobronchial infection 12 weeks after retransplantation.

Three patients developed invasive fungal infections after the discontinuation of secondary voriconazole prophylaxis. One patient (patient 1) had an aspergilloma in the explanted lungs, received antifungal therapy for one month pre-transplant and 34 weeks post-transplant, and developed disseminated mucormycosis 65 weeks after transplant. A second patient (patient 4) had mycetoma in the explanted lungs, received antifungal therapy for 27 weeks post-transplant, and developed pneumonia due to *Dactylaria* 85 weeks after transplant. A third patient (patient 6) had necrotizing pneumonia due to *Penicillium* in the explanted lungs, received antifungal therapy for 30 months pre-transplant and 44 weeks post-transplant, and developed *Aspergillus* pneumonia 100 weeks after transplant.

Overall, two of the six post-transplant fungal infections were caused by a different fungus than implicated in the infections of the explanted lungs (patients 1 and 3). In two cases, it was unclear if the moulds causing the post-transplant infections were the same or different from those infecting the explanted lungs (patients 4 and 10). In only two cases were the post-transplant infections conclusively caused by the same fungus as the infections of the explanted lungs (patients 6 and 12).

The mortality attributable to invasive fungal infections among patients with mould infections of the explanted lungs was 29% (4/14). Among the seven patients with mould infections of the explanted lungs who died following transplant, four died of invasive fungal infections (patients 1, 4, 10 and 12, respectively). Three patients died from bacterial sepsis (patients 5 and 14) or lung allograft failure (patient 2) while receiving voriconazole; there was no evidence of fungal infections in these patients. Among the seven patients who are still alive following transplant,

two are receiving ongoing voriconazole secondary prophylaxis and are currently doing well (patients 9 and 13). Three patients discontinued voriconazole at 7, 30 and 65 weeks (patients 11, 7 and 8, respectively), and are doing well without evidence of fungal infections. The final two patients are alive, having survived a *C. glabrata* endobronchial infection and *A. fumigatus* pneumonia at 12 and 100 weeks, respectively. The patient surviving *A. fumigatus* pneumonia is maintained currently on voriconazole.

Discussion

Fungal infections following lung transplantation have been well-studied, but little is known about the significance of fungal infections in the explanted lungs and their impact upon post-transplant outcomes. To date, there is one report that mycetomas were present in the native lungs of 3% of lung transplant recipients, and they were predictive of poor post-transplant outcomes and death (2). In this earlier study, 67% (4/6) of the deaths among patients with pre-transplant mycetomas occurred within the first month following transplant. Since only one death was attributed to an invasive fungal infection, however, the poor outcomes likely reflected the severity of underlying diseases rather than the direct consequences of the pre-transplant mycetomas. In the present study, we describe the outcomes of lung transplantation among 14 patients with mould infections of the explanted lungs, including 7 patients with chronic necrotizing pneumonias, 3 patients with fungal pneumonias and abscesses, and 4 patients with mycetomas. In addition to being the first report of chronic necrotizing and other forms of fungal pneumonia in the explanted lungs of transplant recipients, our study offers several important insights.

First, underlying mould infections are not uncommon in patients with end-stage lung diseases awaiting transplantation. Five percent (14/304) of patients receiving lung transplants at our institution had histopathologically-proven mould infections in their explanted lungs. Only 21% (3/14) received immunosuppressive agents within one year prior to lung transplantation, suggesting that lung damage itself predisposed them to mould infections. Patients with cystic fibrosis were at a greater risk for a pulmonary mould infection than patients with other lung diseases. This finding is not surprising, since cystic fibrosis patients are frequently colonized with *Aspergillus* spp. (5–8), and allergic bronchopulmonary aspergillosis and aspergilloma have been reported in these patients (8,9). Nevertheless, invasive fungal infections of the lungs were thought to be rare in cystic fibrosis patients who are not immunosuppressed (6). Two of our four cystic fibrosis patients had fungal pneumonias with pulmonary abscesses, and the other two had chronic necrotizing fungal pneumonias. In our series, pulmonary mould infections were also seen in patients with idiopathic pulmonary fibrosis, COPD, and other end-stage lung diseases who were not immunosuppressed. Whereas mycetoma and chronic necrotizing fungal pneumonia are well-described entities in patients with advanced lung diseases, invasive fungal pneumonias with abscesses are less well-recognized. Our findings, therefore, suggest that these types of parenchymal fungal infections should be considered among the spectrum of complications of advanced lung diseases, especially cystic fibrosis.

Second, 57% (8/14) of patients with mould infections in their explanted lungs were not diagnosed or suspected prior to transplantation. The low sensitivity of chest CT in detecting fungal pneumonia in our study might be attributed to the extensive fibrotic, cystic or bronchiectatic changes in our patients' lungs, which could obscure small nodules, cavities or infiltrates. In addition, it is possible that symptoms related to fungal infections were minimal, or attributed to bacterial bronchitis or underlying lung diseases. Taken together, our data suggest that clinicians often overlook fungal infections in a small, but significant percentage of patients with advanced lung disease. Maintaining a level of suspicion, therefore, is essential in improving the diagnosis and treatment of fungal diseases prior to lung transplant. Even with high levels of suspicion, however, clinicians should recognize that the sensitivity of existing

culture-based diagnostic methods is poor. Indeed, we found that bronchial swabs taken at the time of transplantation diagnosed pulmonary fungal infections in only 40% (4/10) of cases, which is consistent with prior reports for the sensitivity of BAL fungal cultures. BAL galactomannan testing was not performed in any of our patients, but we do not believe its routine use would be beneficial. In addition to the fact that the test will not detect non-*Aspergillus* moulds, we previously found that it was not useful in diagnosing pulmonary aspergillosis among non-transplant recipients and was limited by high false-positive rates (10).

Third, patients with mould infections of the explanted lungs were 4 times more likely to develop post-transplant invasive fungal infections than patients without such infections. At our institution, all lung transplant recipients receive voriconazole prophylaxis for 3–6 months following transplant. Among the patients with mould infections of the explanted lungs, the median duration of secondary voriconazole prophylaxis was 10 months. Despite this practice, 43% (6/14) of patients developed invasive fungal infections. Three patients developed breakthrough invasive fungal infections while receiving voriconazole within the first four months of transplant, two of whom had anastomotic site infections. Since voriconazole levels and antifungal susceptibility of moulds were not assessed at UPMC during the study period, it is unclear whether the failures of prophylaxis were due to subtherapeutic serum concentrations, voriconazole-resistant organisms or poor voriconazole penetration into the anastomotic site. Three additional patients developed fungal infections that occurred more than 8 months after the discontinuation of voriconazole. None of these 3 patients were treated with augmented immunosuppression for allograft rejection or bronchiolitis obliterans within the 6 months preceding the diagnosis of fungal infection. Our experience suggests that voriconazole does not eliminate post-transplant invasive fungal infections in patients with mould infections in their explanted lungs, but it may delay the onset of disease in some patients. Of note, 60% (3/5) of long-term survivors without evidence of invasive fungal infections were maintained on secondary voriconazole prophylaxis for at least one year.

Fourth, fungi causing invasive infections after transplant were often different from those infecting the explanted lungs, regardless of when the post-transplant infection occurs. Indeed, the same fungus was conclusively implicated as the cause of both the post-transplant infection and the infection of the explanted lungs in only two patients. Taken with the observations that half the cases occurred over 16 months after transplant and were not associated with recent augmentation of immunosuppression for rejection or bronchiolitis obliterans, the implication of different fungi in pre- and post-transplant infections suggests that intrinsic host factors might predispose at least some patients to invasive fungal infections (11).

The small number of patients limits our ability to draw definitive conclusions about optimal pre- or post-transplant management strategies. Our study suggests that the routine baseline chest CT scan and sputum culture are not sufficient to detect subtle fungal infections in patients with end-stage lung disease. Fungal cultures of sputum should be performed if patients develop respiratory symptoms while awaiting lung transplantation. If the symptoms do not respond appropriately to antibiotics or if sputum cultures grow a fungal pathogen, a high resolution CT scan of the chest and/or BAL should be performed to aid in diagnosis. Physicians should recognize that fungal infections are not uncommon in patients with end-stage lung disease, and keep a high level of suspicion for these entities even if the chest CT or fungal cultures fail to suggest a fungal etiology. Fungal infections diagnosed prior to transplant will require antifungal treatment until respiratory cultures are sterilized and/or improvement of clinical and radiographic parameters is evident.

At the time of transplantation, the explanted lungs of all patients should be inspected carefully for lesions suspicious for infection. Appropriate tissue samples of such lesions should be sent

for comprehensive microbiologic testing including fungal cultures, as well as histopathologic evaluation. Bronchial swabs might complement tissue samples, but are inadequate by themselves. Following transplantation, we recommend a course of secondary voriconazole prophylaxis. The duration of the prophylaxis is currently unclear, but might require several months. Future studies of fungal-specific immune responses at various stages following lung transplantation might identify patients who would benefit from a more prolonged prophylaxis and those in whom prophylaxis might be safely discontinued. Finally, our findings suggest that active fungal infection should be a relative contraindication to lung transplantation. The long-term, fungal disease-free survival of several patients, however, suggests that pre-transplant fungal infections of the lungs need not be an absolute contraindication, particularly in the event of life-threatening lung disease for which other treatment options are exhausted.

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List of abbreviations

UPMC	University of Pittsburgh Medical Center
COPD	chronic obstructive pulmonary disease
CT	computed axial tomography
OB	obliterative bronchiolitis
CXR	chest x-ray

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Table 1

Demographics and clinical data of lung transplant recipients.

	Patients with mould infection in the explanted lungs (n = 14)	Patients with no mould infection in the explanted lungs (n = 290)	P- value
Age median (range)	53	58	NS
Male sex	50% (7)	53% (153)	NS
Smokers	64% (9)	63% (183)	NS
Type of lung transplant:			
- Double lung	93% (13)	61% (176)	0.01
- Single lung	7% (1)	34% (99)	
- Heart-lung	0	5% (15)	
Post-transplant fungal infections:	43% (6/14)	16% (47/290)	0.02
- Tracheobronchitis	2	21	
- Lung parenchymal disease	2	24	
- Disseminated	2	0	
- Others	0	2	
Median/mean time to post- transplant fungal infections (range)	285/326 days (15–697 days)	200/289 days (12–1250 days)	NS

Table 2
Pre-transplant features and post-transplant outcomes of patients with histopathological evidence of mould infections in the explanted lungs

Patient	Age Sex	Underlying lung disease Immunosuppressive therapy pre-transplant	Pre-transplant diagnosis (yes/no) *	Pre-transplant culture (time of culture pre- transplantation)	Explanted lung pathology and culture	Post-transplant antifungal prophylaxis -Duration	Post-transplant fungal infection (onset) - Organism	Outcome *** Duration of follow-up
Mycetoma								
1	68 M	Idiopathic pulmonary fibrosis Prednisone 10 mg daily $\times$ 10 weeks	Yes - CT chest (2 months): fungus ball - Voriconazole and intracavitary amphotericin B (1 month)	<i>A. fumigatus</i> (2 months)	Mycetoma Fungal culture: not performed for	Voriconazole 34 weeks	Proven disseminated infection (65 weeks) - <i>Mucor</i> sp.	Died (fungal infection) 68 weeks
2	56 M	COPD None	Yes - CT chest (6 months): fungus ball - Itraconazole (2 months)	<i>A. fumigatus</i> (5 months)	Mycetoma Culture: <i>A. fumigatus</i>	Voriconazole 2 weeks	No invasive fungal infection	Died (graft failure) 2 weeks
3	19 F	Lung transplant with OB Tacrolimus, mycophenolate, rapamycin, prednisone	No - CT chest (1, 6 and 9 months): negative - CXR (1 month): negative - No antifungal	Negative (6 and 9 months)	Mycetoma Fungal culture: not performed	Voriconazole 77 weeks	Proven endobronchial infection (12 weeks) - <i>C. glabrata</i>	Alive 166 weeks
4	56 M	Idiopathic pulmonary fibrosis None	No - CT chest (11 months): negative - CXR (11 months): negative - No antifungal	Not done	Mycetoma Fungal culture: not performed	Voriconazole 27 weeks	Proven pneumonia (85 weeks) - <i>Dactyaria gallopava</i>	Died (fungal infection) 91 weeks
Necrotizing fungal pneumonia								

Patient	Age Sex	Underlying lung disease Immunosuppressive therapy pre-transplant	Pre-transplant diagnosis (yes/no) * - CT scan - treatment (duration) **	Pre-transplant culture (time of culture pre- transplantation)	Explanted lung pathology and culture	Post-transplant antifungal prophylaxis -Duration	Post-transplant fungal infection (onset) - Organism	Outcome *** Duration of follow-up
5	32 M	Cystic fibrosis None	Yes - CT chest (3 months): negative - CXR (3 months): negative Voriconazole (2 months)	<i>A. fumigatus</i> (3 months)	Necrotizing fungal pneumonia Culture : <i>A. fumigatus</i>	Voriconazole 30 weeks	No invasive fungal infection	Alive 108 weeks
6	38 F	Lung transplant with OB Tacrolimus, mycophenolate, rapamycin, prednisone	Yes - CT chest (2 months): multiple lung cavities - Voriconazole (14 months)	Negative (4 days) Cytology of BAL showed fungal hyphae	Necrotizing pneumonia Fungal culture: not performed	Voriconazole 77 weeks	No invasive fungal infection	Died (bacterial sepsis) 77 weeks
7	60 F	COPD None	Yes - CT-chest (4 months): multiple lung nodules - Voriconazole (30 months)	<i>A. fumigatus</i> (33 months)	Necrotizing pneumonia Culture: <i>Penicillium</i> <i>spp.</i>	Voriconazole 44 weeks	Proven pneumonia (100 weeks) - <i>A. fumigatus</i>	Alive 135 weeks
8	47 F	Bronchiectasis None	No - CT chest (8 months): negative - CXR (1 month): negative - No antifungal	Negative (1 month)	Necrotizing fungal pneumonia Fungal culture: negative	Voriconazole 65 weeks	No invasive fungal infection	Alive 81 weeks
9	47 F	Cystic fibrosis None	No - CT chest (2 months): negative - CXR (2 months): negative - No antifungal	Not done	Necrotizing fungal pneumonia Fungal culture: negative	Voriconazole 72 weeks	No invasive fungal infection	Alive 72 weeks

Patient	Age Sex	Underlying lung disease Immunosuppressive therapy pre-transplant	Pre-transplant diagnosis (yes/no) *	Pre-transplant culture (time of culture pre- transplantation)	Explanted lung pathology and culture	Post-transplant antifungal prophylaxis -Duration	Post-transplant fungal infection (onset) - Organism	Outcome *** Duration of follow-up
10	55 F	Multiple connective tissue disease None	No - CT chest (8 months) negative - CXR (12 hours): negative - No antifungal	Not done	Necrotizing fungal pneumonia Fungal culture: negative	Voriconazole 20 weeks	Proven endobronchial infection (2 weeks) - Culture grew <i>Penicillium</i> sp., and histopathology showed invasive hyphae.	Died (fungal infection) 21 weeks
11	58 M	COPD None	No - CT chest (5 months) negative - CXR (5 months): negative - No antifungal	Not done	Necrotizing fungal pneumonia Fungal culture: negative	Voriconazole 7 weeks	No invasive fungal infection	Alive 184 weeks
Fungal pneumonia								
12	26 F	Cystic fibrosis None	Yes - CT chest (16 months): negative - CXR (16 months) : - Voriconazole and terbinafine (5 months)	<i>S. inflatum</i> (consistently positive for at least 24 months) <i>A. fumigatus</i> (2 months)	Fungal pneumonia with abscess Culture: <i>Scedosporium inflatum</i>	Voriconazole and terbinafine 17 weeks	Proven disseminated infection (17 weeks) - <i>Scedosporium inflatum</i>	Died (fungal infection) 17 weeks
13	52 M	Cystic fibrosis None	No - CT chest (10 months): negative - CXR (10 months): negative - No antifungal	Not done	Fungal pneumonia with abscess Fungal culture: negative	Voriconazole 144 weeks	No invasive fungal infection	Alive 144 weeks
14	63 M	COPD None	No - CT chest (2 months): negative	Not done	Fungal pneumonia with abscess Fungal culture: negative	Voriconazole 42 weeks	No invasive fungal infection	Died (bacterial sepsis) 42 weeks

Patient	Age Sex	Underlying lung disease Immunosuppressive therapy pre-transplant	Pre-transplant diagnosis (yes/no) *	Pre-transplant culture (time of culture pre- transplantation)	Explanted lung pathology and culture	Post-transplant antifungal prophylaxis -Duration	Post-transplant fungal infection (onset) - Organism	Outcome *** Duration of follow-up
			- CT scan - treatment (duration) ** - CXR (2 months); negative - No antifungal					

* CT scan performed before lung transplantation (time frame indicates the most recent CT scan that was performed before lung transplantation)

** Duration of anti-fungal treatment prior to transplantation.

*** Cause of death if the patient expired.

All patients received double lung transplantation except for patient 1.

COPD = chronic obstructive pulmonary disease; OB = obliterative bronchiolitis; CXR = chest x-ray; CT = computerized tomography.