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Fusarium Infection in Lung Transplant Patients:

Report of 6 Cases and Review of the Literature

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Abstract

Fusarium is a fungal pathogen of immunosuppressed lung transplant patients associated with a high mortality in those with severe and persistent neutropenia. The principle portal of entry for *Fusarium* species is the airways, and lung involvement almost always occurs among lung transplant patients with disseminated infection. In these patients, the immunoprotective mechanisms of the transplanted lungs are impaired, and they are, therefore, more vulnerable to *Fusarium* infection. As a result, fusariosis occurs in up to 32% of lung transplant patients. We studied fusariosis in 6 patients following lung transplantation who were treated at Massachusetts General Hospital during an 8-year period and reviewed 3 published cases in the literature. Cases were identified by the microbiology laboratory and through discharge summaries. Patients presented with dyspnea, fever, nonproductive cough, hemoptysis, and headache. Blood tests showed elevated white blood cell counts with granulocytosis and elevated inflammatory markers. Cultures of *Fusarium* were isolated from bronchoalveolar lavage, blood, and sputum specimens.

Treatments included amphotericin B, liposomal amphotericin B, caspofungin, voriconazole, and posaconazole, either alone or in combination. Lung involvement occurred in all patients with disseminated disease and it was associated with a poor outcome. The mortality rate in this group of patients was high (67%), and of those who survived, 1 patient was treated with a combination of amphotericin B and voriconazole, 1 patient with amphotericin B, and 1 patient with posaconazole. Recommended empirical treatment includes voriconazole, amphotericin B or liposomal amphotericin B first-line, and posaconazole for refractory disease. High-dose amphotericin B is recommended for treatment of most cases of fusariosis. The echinocandins (for example, caspofungin, micafungin, anidulafungin) are generally avoided because *Fusarium* species have intrinsic resistance to them. Treatment should ideally be based on the *Fusarium* isolate, susceptibility testing, and host-specific factors. Prognosis of fusariosis in the immunocompromised is directly related to a patient's immune status. Prevention of *Fusarium* infection is recommended with aerosolized amphotericin B deoxycholate, which also has activity against other important fungi.

INTRODUCTION

Lung transplantation is now a viable and widely accepted treatment of end-stage lung disease. The first lung transplant was carried out in 1963 as a single left lung transplant from a cadaver where the recipient survived just 18 days, eventually succumbing to renal failure and malnutrition.[36,37] From that time until the early 1980s, the main problems facing lung

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transplantation were organ rejection and healing of airway anastamoses. Advances during the early 1980s saw the advent of cyclosporine A, a potent immunosuppressive drug, and improved surgical techniques. This led to the first successful heart-lung transplant for idiopathic pulmonary artery hypertension in 1981, single lung transplant for idiopathic pulmonary fibrosis in 1983, and double lung transplant for emphysema in 1986.[21,96,119] From January 1, 1988, to September 30, 2009, 471,304 single lung transplantations have been carried out the United States alone.[120] Some diseases that cause respiratory failure and may ultimately benefit from lung transplantation include suppurative diseases like chronic obstructive airways disease, bronchiectasis, chronic bronchitis, and cystic fibrosis, and nonsuppurative diseases like emphysema, idiopathic pulmonary fibrosis, primary and secondary pulmonary hypertension, alpha-1 antitrypsin disease, Good-pasture disease, sarcoidosis, rheumatoid disease, hemosiderosis, occupational lung disease, and inhalation burns.[83,117] Lung transplantation is considered when life expectancy is less than 24–36 months and patients have New York Heart Association (NYHA) class III and IV symptoms.[69]

Lung transplantation is often complicated by bacterial and fungal infections.[45] Invasive fungal infections are serious and potentially life-threatening complications of lung transplantation, occurring in 14%–32% of recipients.[15,45,51] Fungal pneumonias are a significant contributor to the 35% of pneumonia deaths in the first year following lung transplantation.[1,17] In this group of patients the epidemiology of fungal infections has changed with the use of fluconazole prophylaxis; there has been a significant decrease in the incidence of yeast infections, namely *Candida* species, and an increase in mold infections.[4,15,64,112,124] Among these mold infections the incidence of invasive *Fusarium* species infections is rising, now second only to *Aspergillus* species.[15,73,77,106,112] The diagnosis of invasive fusariosis currently has a very poor prognosis.[50] Early diagnosis and treatment are essential to improve the chances of survival. Given the magnitude and severity of the problem, surprisingly little is known about the pathogenesis, clinical characteristics, laboratory diagnosis, and management of fusariosis.[15]

The main factors contributing to the acquisition of invasive fusarial infections in lung transplant patients are the following: 1) the protective physical barriers to infection in the lungs are compromised during lung transplantation; 2) the protective mucociliary clearance and cough reflexes are reduced due to denervation of the transplanted lung; 3) the transplanted lung is continuously exposed to the open environment and its microorganisms; 4) patients are immunosuppressed with potent pharmacologic agents; and 5) the incidence of infections caused by drug-resistant and aggressive strains of fungi is increasing.[17,53,59,64,65] Note that *Fusarium* species can be acquired from the environment by the recipient following transplantation, or alternatively *Fusarium* species can be present as a pretransplant colonizing organism in the donor lung that can manifest following transplantation, causing clinical disease in the recipient.[17] The main entry site for *Fusarium* species is the airways via inhalation of airborne conidia, and the lungs are involved in 31%–41% of all fusariosis cases.[33,68,127] In support of this is the development of sinusitis and pneumonia in the absence of fungemia.[75] Lung involvement can also occur following hematongenous spread of the fungus, which almost always occurs in the immunocompromised.[75]

To better understand the emerging role of this pathogen in lung transplant patients, we here examine the clinical characteristics of *Fusarium* infections in this patient population and evaluate possible risk factors, clinical findings, laboratory diagnosis, response to therapy, and outcomes from clinical cases and the literature.

METHODS

Clinical Data Collection

Six cases of *Fusarium* infection in lung transplant patients were identified in our institution (Massachusetts General Hospital) by the microbiology laboratory and from discharge summaries. The review period was from January 2001 to November 2008 inclusive; over this time, a total of 73 lung transplants were carried out at Massachusetts General Hospital.[120] Data for these cases were obtained from a detailed study of computerized patient medical records. In addition, we reviewed the English-language literature to identity similar cases of fusariosis in lung transplant patients, searching the MEDLINE database (National Library of Medicine, Bethesda, MD) using the key words “transplant” and “Fusarium.” We did not constrain the search to any specific time period due to the limited number of published case reports.

Identification and Determination of MIC of *Fusarium* Species

The *Fusarium* isolate from Patient 6 (Tables 1 and 2) was obtained and the species was identified by amplifying and sequencing a portion of the translation elongation factor (TEF) 1α coding region as described by O’Donnell et al.[80] The minimum inhibitory concentration (MIC) of the isolate was determined spectrophotometrically using RPMI 1640 media (Mediatech, Inc., Manassas, VA) following the Clinical and Laboratory Standards Institute microbroth dilution method. All antifungal compounds tested were obtained from Sigma-Aldrich (St. Louis, MO), with the exception of caspofungin (Merck, Whitehouse Station, NJ).

RESULTS

Case Series

We identified 6 lung transplant patients with fusariosis (mean age, 42.6 yr; range, 19–66 yr) (Table 1). The reasons for lung transplant were cystic fibrosis (2 patients), interstitial pulmonary fibrosis (2 patients), alpha-1 antitrypsin deficiency (1 patient), and chronic obstructive pulmonary disease (1 patient). The patients with cystic fibrosis had bilateral lung transplants, while the others had single lung transplants (2 patients with left lung transplants and 2 patients with right lung transplants). All 4 patients with single lung transplants had clinical and radiologic evidence of infection in the transplanted lung. Only 1 of 6 patients had acute rejection of their transplants before *Fusarium* infection. Importantly, 4 of the 6 patients had fungal infections with other organisms before infection with *Fusarium*. All patients were on a combination of 2 or more immunosuppressive drugs, and 3 of the 6 patients were on antifungal prophylaxis.

Clinical findings included shortness of breath in 4 of the 6 patients, fever in 5 of the 6 patients (range, 36.6°C to 37.9°C), nonproductive cough in 2 of the 6 patients, hemoptysis in 1 of the 6 patients, and headache in 2 of the 6 patients. Clinical examination findings included crackles in 4 of the 6 patients, expiratory wheeze in 1 of the 6 patients, and reduced breath sounds on the affected side in 2 of the 6 patients. Interestingly, there was no sinus involvement in any of the patients. All patients had evidence of infection on chest radiographs and computed tomography (CT) scans.

Laboratory findings included an elevated white blood cell count in 2 of the 6 patients (white cell count range, 4.9–19.2 × 10^9 L^{-1}) and granulocytosis in 5 of the 6 patients (polymorphonuclear cells range, 75%–94%). *Fusarium* was identified in bronchoalveolar lavage (BAL) cultures in 5 of 6 patients, blood cultures in 1 of 6 patients, and sputum cultures in 1 of 6 patients; 2 of 6 patients had septated fungal hyphae recognized by

microscopy. Infections were within a year of lung transplantation in 4 of 6 patients, a little over 2 years in 1 patient, and over 15 years in the remaining patient. As noted above, all patients had concomitant infections with various organisms (Table 2); 2 of 6 patients had positive 1→3 β-D-Glucan (BDG) and galactomannan tests, while 1 of 6 patients had a lone positive galactomannan test (Table 1).

All 6 patients had radiologic investigations including chest radiographs and CT scans. In each case, there was evidence of lung involvement (Figure 1). Of the radiologic investigations that were formally reported by a radiologist, the following features were listed: consolidation (1 patient), atelectasis (1 patient), nodular opacities (2 patients), mediastinal lymphadenopathy (1 patient), pleural effusions (2 patients), ground glass opacities (1 patient), and bronchiectasis (2 patients). Note that each patient had some, but not all, of these features.

Liposomal amphotericin B and caspofungin were used to treat 1 of 6 patients, liposomal amphotericin B and voriconazole in 2 of 6 patients, amphotericin B and voriconazole in 1 of 6 patients, and voriconazole alone in 1 of 6 patients. One patient did not receive treatment for fusariosis. The patient treated with amphotericin B and voriconazole was the sole survivor and was alive more than a year after infection; the other 5 patients all succumbed to the infection.

Literature Review

We identified 3 patients with *Fusarium* infection following a lung transplant reported in the English-language literature for which adequate clinical data were available.[9,35,41] The mean age of infection was 44.3 years (range, 18–62 yr) (Table 3). The reasons for lung transplantation included advanced bullous emphysema in 1 patient, emphysema due to alpha-1 antitrypsin deficiency and tobacco use in 1 patient, and cystic fibrosis in the remaining patient. The patient with cystic fibrosis had a double lung transplant, while the other 2 patients had a single right lung transplant. All 3 patients were on a combination of 3 immuno-suppressive agents when they developed *Fusarium* infections: prednisolone, azathioprine, and cyclosporine.

Clinical findings included shortness of breath in 1 of 3 patients, fever in 2 of 3 patients, productive cough in 2 of 3 patients, pleuritic chest pain in 1 of 3 patients, asthenia in 1 of 3 patients, and weight loss in 1 of 3 patients. There were no signs of sinus involvement in these patients. All 3 patients had evidence of infection on chest radiographs and CT scans.

Laboratory findings included normal white cell counts in all 3 patients. *Fusarium* was identified on BAL cultures in 2 of 3 patients, sputum cultures in 1 of 3 patients, and blood cultures in 1 of 3 patients. All 3 patients developed fusariosis soon after lung transplantation. Two of the 3 patients were infected with *F. solani*, while the other patient was infected with *F. proliferatum*. MIC data were available for 2 of 3 patients (Table 4). Both of these isolates were resistant to fluconazole and susceptible to amphotericin B.

Amphotericin B was used to treat 1 of the 3 patients, liposomal amphotericin B in 1 of the 3 patients, and posaconazole in 1 of the 3 patients. The patient treated with liposomal amphotericin B died, while the others survived.

DISCUSSION

Fusarium organisms are filamentous fungi found in the soil and air worldwide, especially in tropical and temperate regions.[71,130] They are mainly plant pathogens but occasionally cause severe infection in farm animals.[28,71,75] *Fusarium* causes a wide range of disease in humans

including superficial, locally invasive, and disseminated infections and allergic disease; fusarial mycotoxins have been linked to food poisoning, pancytopenia, and esophageal cancer.[71,74,75,107,129] Although many species of *Fusarium* exist, most of the clinical isolates belong to 3 groups: the *Fusarium solani* species complex (FSSC), the *Fusarium oxysporum* species complex, and the *Gibberella fujikuroi* species complex. Isolates from the FSSC are responsible for a majority of the *Fusarium* mycoses, and at least 20 phylogenetically distinct species of the FSSC have been isolated from clinical specimens.[81] Clinical isolates of FSSC members are phylogenetically similar to isolates from other environmental sources, suggesting that human infections are the result of a susceptible host contacting the FSSC isolate in the environment.[131] *F. oxysporum* isolates are the second most common cause of *Fusarium* infections, and a single clonal widespread lineage is responsible for most *F. oxysporum* infections.[82] Several members from the *G. fujikuroi* species complex are able to infect humans, most notably *F. verticillioides (F. moniliforme)* and *F. proliferatum*.[79]

Disseminated infections usually occur only in patients with severe and persistent neutropenia.[75] Clinicians are increasingly aware of *Fusarium* as an important pathogen of immunocompromised patients associated with high mortality.[15,29,74] Of note, *Fusarium* species and *Aspergillus* species are often confused because they have similar histologic appearances with septate branching hyphae and they can cause similar clinical syndromes.[38,115] Some patients are consequently started on amphotericin B, an agent used to treat aspergillosis but with little activity against some *Fusarium* species.[5,6,49,81,97,122] It is, therefore, important to make the correct diagnosis to optimize treatment and improve prognosis.[29]

Epidemiology and Clinical Spectrum

The clinical manifestation of fusariosis depends on the patient's immune status and the source of the infection. In immunocompetent hosts, there is a broad spectrum of infection ranging from keratitis with contact lens use, peritonitis in patients with intraabdominal catheters, to sinusitis, pneumonia, thromboplebhitis, endophthamitis, fungemia, septic arthritis, and osteomyelitis.[14,26,30,46,47,52,58,70,74,75,92,99,105,114] Immunocompromised patients with prolonged and extreme neutropenia and severe T-cell immunodeficiency, such as lung transplant patients, are those most at risk of developing fusariosis.[15] They develop similar infections to those in immunocompetent patients but generally have more locally invasive or disseminated fusarial infections.[74,75]

The main site of entry for *Fusarium* species in lung transplant patients is the airways by inhalation of fusarial conidia followed by areas of skin and mucosal membrane breakdown.[75] *Fusarium* is ubiquitous in the environment and fusarial conidia have been detected in outdoor air samples.[7,15,66] One study[18] found *Fusarium* to be more prevalent in air samples than *Aspergillus. Fusarium* species have also been isolated from indoor water storage systems and outdoor water bodies. Water-related activities, such as showering and outdoor water sports, can aerosolize fusarial conidia, thereby making them airborne and facilitating transmission through the airways.[75,82]

The lungs are involved in the majority of cases of disseminated fusariosis in lung transplant patients.[75] Even after controlling for immune status, lung involvement is associated with a higher mortality.[76] Lung lesions in fusarial pneumonia include nodular and cavitary lesions and nonspecific alveolar or interstitial infiltrates.[76] The clinical picture is usually non-specific, with shortness of breath, nonproductive cough, and pleuritic chest pain.[75,76]

Our results conform with those reported above in the literature. In the current case series, 2 patients had disseminated fusariosis with positive blood cultures, and both these patients had lung involvement with positive BAL samples. Furthermore, all 9 lung transplant patients

studied had proven lung involvement with positive BAL samples or sputum cultures and radiologic evidence of infection. There was a high mortality rate (67%) for this group of patients.

Lung transplant recipients are at high risk for other molds that are clinically, histopathologically, and radiologically very similar to fusariosis. This group of patients is susceptible to infection with *Aspergillus* species and other molds such as Zygomycetes, *Scedosporium*, and dematiaceous molds.[67,108,109] We will briefly touch on 2 of the most common mold infections, *Aspergillus* and Zygomycetes, but these have been covered elsewhere in more detail.[22,43,72,85,87,100] The incidence of invasive *Aspergillus* infections in lung transplant patients is between 6% and 16% with a high mortality rate.[22,108,109] The risk factors for developing aspergillosis are largely the same as those listed above for developing fusariosis, and the clinical presentation of aspergillosis is similar to that of fusariosis with the exception of skin lesions and myalgia occurring more commonly in fusariosis.[22] Furthermore, the radiologic features of aspergillosis are similar to those of fusariosis, with subpeural nodular opacities and cavitation.[22] Lung transplant patients can develop *Aspergillus* infections anytime from months to years after the lung transplant, but the majority of cases are diagnosed within 6 months of the transplantation.[67,109]

The most common non-*Aspergillus* molds that colonize airways in lung transplant recipients include *Cladosporium*, *Phialemonium,* and Zygomycetes.[108] Zygomycetes are ubiquitous filamentous fungi that can also cause life-threatening infection in lung transplant patients.[22,100] Risk factors for zygomycosis includes immunosuppression, malignancy, diabetes mellitus, injection drug use, prematurity, receiving deferoxamine therapy, and long-term prophylaxis with voriconazole.[22,100,108] Pulmonary disease is most common in immunocompromised patients, and the most common causative organisms include, from most common to least common, *Rhizopus* species, *Mucor* species, and *Cunninghamella bertholletiae*, among others.[22,100] Common symptoms include fever, dyspnea, chest pain, rhinocerebral infection, and multi-organ failure.[113] Like fusariosis, radiologic features include subpleural lung nodules.[113]

Diagnosis

Diagnosis of fusariosis usually depends on both the clinical and laboratory findings. The following criteria can be used to discern true infection in lung transplant patients:

1. isolation of several colonies of *Fusarium* from the same specimen or isolation of the same fungus from different specimens;
2. positive identification of the fungus on direct visualization of laboratory samples; and
3. isolation of *Fusarium* from a site that is more likely to indicate infection than not.[75] (For example, *Fusarium* identified in a sputum sample from a healthy immunocompetent patient may be the result of recent inhalation of conidia; however, *Fusarium* isolated from a BAL culture from an immunosuppressed transplant patient should be considered diagnostic of infection, and antifungal therapy initiated.)

Blood cultures are frequently positive in fusariosis, unlike aspergillosis, because *Fusarium* species sporulate, which facilitates bloodborne dissemination and growth.[56,75] Confirmation of fusariosis may require histopathology, polymerase chain reaction (PCR), or mass spectrometry. A significant problem with histopathologic diagnosis is that biopsy specimens are sometimes hard to obtain, especially in patients who are critically ill. Furthermore, morphologic discrimination between *Fusarium* and *Aspergillus* is highly subjective and

difficult because their hyphae appear very similar on direct visualization. Finding hyphae and spores in tissue samples from lung transplant patients is highly suggestive of fusariosis. Distinguishing *Fusarium* from other fungi may also require in situ hybridization in paraffin-embedded tissue specimens.[38,75] In the current study, only 2 of the 6 patients had positive fungal stains on microscopy with septate hyphae.

Culture methods typically have a low sensitivity for identifying *Fusarium*, although the fungus can be identified by its microscopic appearance.[48] Species identification may be difficult and may require the use of molecular techniques, and fortunately, PCR-based methods are now available to identify *Fusarium* species from culture media, blood, and tissue.[39,44] The detection of *Fusarium* from blood cultures, however, has poor sensitivity, and species identification is complex and requires a great deal of time and expertise.[40,75,128] Furthermore, using the TEF1α gene as a target for species identification remains questionable in some *Fusarium* species.[62] Some traditional PCR assays use the internal transcribed spacer (ITS) region between the 18S rDNA and 28S rDNA, which has high specificity for certain *Fusarium* strains such as *F. proliferatum*, and a combination of several other conserved sequenced regions as the current best molecular method to identify *Fusarium* isolates to the species level.[107]

Molecular markers of fungal infection, such as BDG and galactomannan, can also be used to help diagnose infection. BDG is a nonspecific marker of fungal infection that is usually positive in invasive fusariosis. However, this assay cannot distinguish between *Fusarium* and other fungi.[78,84] A positive BDG test and a negative galactomannan test in a lung transplant patient with a mold infection is highly suggestive of *Fusarium* infection.[75] In the current study, 2 patients had a positive BDG test and a negative galactomannan test, while another patient had a lone positive galactomannan test (defined as a test result of > 0.5).[10,88]

Khan et al[48] evaluated the diagnostic usefulness of a BDG test and DNA detection using a highly sensitive and specific nested PCR method on serum and BAL specimens from mice infected with *F. oxysporum*. They found that the BDG and PCR sensitivity in BAL and serum samples were 15 and 98%, and 92 and 75%, respectively. When combining the 2 tests for serum samples the sensitivity rose to 98% with a negative predictive value of 92%. The specificity and positive predictive value were 100% for both serum and BAL specimens. Of note, however, the BDG test remained positive throughout the infection period, while a positive PCR result declined over time. Nonetheless, combining the BDG and PCR tests on serum promises to be a highly sensitive and specific diagnostic method for invasive *Fusarium* infection. There is, however, a lack of published data in human subjects to validate this hypothesis.

The use of mass spectrometry to identify clinical isolates of *Fusarium* has recently gained popularity. Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) is a tool that has been used to characterize fungi.[19,55,121,126] At the moment, though, there is no standard protocol or validated database to use as a benchmark.[62] A major advantage of mass spectrometry is that fungal identification can be completed in 1 hour compared to culture-based methods, which require serial subcultures and microscopic examination of morphologic characteristics that usually take over a week to yield results. PCR-based methods take a minimum of 2 days to yield results. Other advantages to using MALDI-TOF analysis are that each run can include many species and strains of fungi, the results are very consistent, and it is cost efficient.[62,107]

Treatment

The increase in the incidence of severe fusarial infections and the rapid progression of disease demands early and aggressive treatment of patients with disseminated and invasive

infections.[115] The management of fusariosis includes conservative medical and surgical measures. Conservative measures include removal of indwelling lines and central venous catheters in patients with confirmed catheter-related fungemia, while surgical measures include debulking of necrotic and infected tissue in locally invasive disease.[15,57,75,123] In addition, adjunctive therapies exist and can be used to optimize management of these patients.[60,75,93,101]

There are currently inconsistent and conflicting recommendations in the literature with regards to the treatment of fusariosis. In the current study, monotherapy with voriconazole, amphotericin B, liposomal amphotericin B, and posaconazole, or dual combination therapy with liposomal amphotericin B and caspofungin, liposomal amphotericin B and voriconazole, and amphotericin B and voriconazole were used for treatment. Mortality was high in this group of patients (67%), and of those who survived, 1 patient was treated with a combination of amphotericin B and voriconazole, 1 patient with amphotericin B, and 1 patient with posaconazole. In general, however, voriconazole is the recommended first-line treatment, with amphotericin B, its lipid formulation, and posaconazole as possible alternatives.[2,60,75,102] The echinocandins (for example, caspofungin, micafungin, anidulafungin) are avoided because *Fusarium* species have intrinsic resistance to the echinocandins.[8,25] In a study of 273 patients with refractory invasive fungal infections caused by *Candida* species, *Aspergillus* species, *Fusarium* species, *Scedosporium* species, *Cryptococcus neoformans*, and *Penicillium* species, and 28 patients requiring primary treatment of their fungal infections, treatment with voriconazole was associated with a good response in 50% of patients and 45.5% (5 of 11 patients) of patients with fusariosis.[8,91] Voriconazole was well tolerated as <10% of the patients required a reduction in dose or removal from voriconazole therapy. Voriconazole is approved by the United States Food and Drug Administration for salvage therapy, and posaconazole can also be used as salvage therapy for refractory invasive fusarial infections.[8,60,95,111] Should either of these newer generation triazoles be chosen for *Fusarium* treatment, they require therapeutic drug monitoring. Variability in plasma drug levels are associated with drug interactions, patient age, nonlinear pharmacokinetics, polymorphisms of the cytochrome P450 CYP2C19 gene, and variable enteral absorption of drugs.[60] A plasma concentration of voriconazole below 1 mg/L is likely to be subtherapeutic, and above 5 mg/L there is neurologic toxicity.[86] The therapeutic levels of voriconazole are not, however, well defined, and a clinical response should be taken into account. The MIC of voriconazole for *Fusarium* species varies widely and is between 0.25–8 mg/L.[8] Therefore, the initial target level for voriconazole should be between 1 and 5 mg/L watching for a clinical response. If there is no clinical response, the levels should be increased up to 8 mg/L while monitoring for side effects. If there are side effects or if there is no clinical response at 8 mg/L, therapy should be switched to a second-line agent.

Isavuconazole, formerly BAL4815, is a new broad-spectrum triazole antifungal in the late stages of clinical testing. Guinea et al[34] compared the in vitro activity of isavuconazole to that of voriconazole and fluconazole. The MIC_{50} for isavuconazole and voriconazole were both 16 mg/L, and the MIC_{90} were 16 mg/L and 4 mg/L against *Fusarium* species, respectively. This shows that isavuconazole and voriconazole have similar but limited activity against the *Fusarium* species tested.

Naturally, the treatment of fusariosis should depend on the type of infection, the *Fusarium* isolate, its susceptibility to antifungals, and host-specific factors. However, given the difficulties in laboratory identification, the species of *Fusarium* is not always known, let alone the antifungal susceptibilities. At present, amphotericin B and its lipid formulation appear to be better than the newer triazoles (voriconazole, posaconazole, ravuconazole, albaconazole) against *F. oxysporum* and *F. solani*.[8,111,125] O'Donnell et al[81] tested 19 FSSC

isolates with 10 antifungals and terbinafine, a synthetic allylamine antifungal, and amphotericin B showed the lowest MICs. Amphoterin B, though, has clinically poor activity and renal toxicity.[103]

Ruiz-Cendoya et al[103] studied the interaction between the new triazoles (voriconazole and posaconazole) with amphotericin B in mice infected with *F. oxysporum*. Monotherapies of each antifungal agent showed very poor efficacy in vivo. There was a poor response to the combination of amphotericin B and voriconazole; however, there was a much better response to the combination of amphotericin B and posaconazole.[103] The poor efficacy of the amphotericin B and voriconazole combination has been reported in clinical studies, although 2 published cases report that this combination of antifungals led to clinical improvements in patients with *F. solani* infections before the resolution of neutropenia.[42,75,101,102] This combination was tested in mice infected with *F. solani* and showed only modest treatment efficacy.[102] Posaconazole shows high MICs for *Fusarium* species in general, but it is better against *F. oxysporum* than *F. solani*.[3,8,116] One case report described poor efficacy using combination amphotericin B and posaconazole, although the level of posaconazole was subtherapeutic due to the patient's poor diet.[54]

Azor et al[11] studied the susceptibility of *F. verticillioides* and *F. thapsium* to antifungals. *F. verticillioides* commonly causes fusariosis in humans. The results showed that terbinafine was most effective in treating *F. verticillioides* in vitro. In decreasing order of potency against *F. verticillioides*, terbinafine was followed by posaconazole, ravuconazole, voriconazole, amphotericin B, ketoconazole, albaconazole, and itraconazole.[11] Again, terbinafine was the most effective drug in vitro in treating *F. thapsium*. Voriconazole and amphotericin B followed with equal potencies. The other antifungals tested showed no activity again *F. thapsium*.

The treatment of other molds differs from the treatment of fusariosis in some important ways. Amphotericin B deoxycholate has broad-spectrum activity against *Aspergillus* species and Zygomycetes.[22,104] Liposomal amphotericin B has the same spectrum of activity but fewer side effects. Concerning the azoles: fluconazole is not active against molds; itraconazole has good in vitro activity against *Aspergillus* but not *Fusarium* or Zygomycetes; voriconazole has good activity against most *Aspergillus* species but no activity against Zygomycetes; and posaconazole has good in vitro activity against *Aspergillus* and Zygomycetes.[13,20,22,31,94,104] Caspofungin, anidulafungin, and micafungin all have some activity against *Aspergillus* but are not effective in monotherapy against invasive aspergillosis and have little or no activity against Zygomycetes.[13,22,25,27]

In treating lung transplant patients with fusariosis, antifungal therapy should be complemented by reversal of as many underlying predisposing factors as possible. Low neutrophil and macrophages counts are 2 such predisposing factors to *Fusarium* infection, which can be treated with immunotherapy.[60] Immunotherapy includes growth factors (granulocyte colony-stimulating factor [G-CSF] and granulocytemacrophage colony-stimulating factor [GM-CSF]) and granulocyte transfusions for neutropenic patients, and gamma interferon and/or GM-CSF for patients with adequate neutrophil counts.[75] There is, however, a lack of clinical data on the role of immune reconstitution in *Fusarium* infection, and the best treatment strategy remains unclear. Because of the poor prognosis of fusariosis, especially in lung transplant patients with profound and prolonged neutropenia, G-CSF and granulocyte transfusions are often given.[75,101] Immunotherapy is well tolerated.[93] To our knowledge, there is currently only 1 case report in the literature of successful treatment of invasive fusariosis with a combination of pharmacologic treatment and immunotherapy.[75,101]

The response to treatment in lung transplant patients can be assessed by 1) disappearance of fevers and other clinical signs of infection, 2) resolution of fungemia, and 3) attenuation of radiologic features of the disease.[75] Note that radiologic features of infection may persist making, their interpretation difficult. Positron emission tomography (PET) and indium-labeled white blood cell scintigraphy can be used to detect inflammation if necessary.[12,61,75]

Prognosis

The prognosis of fusariosis in lung transplant patients is directly related to the immune status of the patient, with high mortality rates in patients with prolonged and profound neutropenia. Multivariate predictors of poor outcome include persistent neutropenia, recent corticosteroid therapy, disseminated disease, and lung involvement. Those with no risk factors or whose only risk factor is corticosteroid therapy have statistically significant higher survival rates.[75_77] In the current study, all 9 lung transplant patients had some predictors of a poor outcome listed above. The mortality rate in this patient group was high (67%), which was consistent with trends published in the scientific literature.

Prevention

Given the poor prognosis of fusariosis and the limited susceptibility to antifungals, prevention of infection is better than the cure. Precautions should be taken to prevent lung transplant patients from coming in contact with known sources of *Fusarium*.[75] Decreasing the level of immunosuppression should be attempted where possible, especially in patients with a prior history of fusariosis. In addition, active infections, such as skin lesions, should be treated before commencing immuno-suppressive therapy.[74,75]

Antifungal prophylaxis should be based on local or organism-specific patterns of susceptibility. Prophylactic antifungals reduce mortality and the incidence of fungal infections in lung transplant patients.[32,45] Yet there is no standardized approach to antifungal prophylaxis. Husain et al[45] surveyed 50 lung transplant centers worldwide, where roughly 63% of all lung transplants are carried out. They found that aerosolized amphotericin B deoxycholate alone or in combination with itraconazole was the most common prophylaxis strategy used with good results. Itraconazole itself has poor in vitro activity against *Fusarium* species.[16,110] Nevertheless, the use of aerosolized amphotericin B deoxycholate with itraconazole might be a more appropriate approach because it has good activity against *Aspergillus* species, *Fusarium* species, and *Candida* species, among others.[2,23,60,63,89,90,98] The drug-drug interactions associated with itraconazole should, however, be taken into account. Other prophylactic strategies used with some success to prevent fungal infections in general include single drug dosing with liposomal amphotericin B, fluconazole, voriconazole, posaconazole, and oral nystatin.[24,60,98,118] Limitations to antifungal prophylaxis include selection of resistance, drug toxicity and interactions to the patient, high cost, and interference with some diagnostic assays.[45]

Conclusions

The *Fusarium* species is an important but relatively uncommon pathogen of immunocompromised lung transplant patients associated with a high mortality rate. *Fusarium* species that infect lung transplant patients most frequently are *F. solani, F. oxysporum, F. verticillioides*, and *F. proliferatum*. The principle portal of entry for *Fusarium* species is the airways, followed by the sites of skin breakdown and possibly mucosal membranes. The presentation of fusariosis depends on the immune status of the host and the portal of entry. In humans, *Fusarium* causes a wide range of disease including superficial, locally invasive, and disseminated infections and allergic disease, and its toxins are associated with food poisoning, pancytopenia, and esophageal cancer. In the lungs, the *Fusarium* organism causes a nonspecific illness with shortness of breath, nonproductive

cough, and pleuritic chest pain. Laboratory confirmation of fusariosis is based on fungal cultures, microscopy, BDG test, galactomannan test, and PCR. Laboratory diagnosis would benefit greatly from MALDI-TOF mass spectrometry, which is a versatile, reliable, and cost-effective assay. Treatment should ideally be based on the *Fusarium* isolate, susceptibility testing, and host-specific factors. The current recommendations for treating fusariosis empirically in lung transplant patients are voriconazole, amphotericin B, or liposomal amphotericin B first-line and posaconazole for refractory disease. The echinocandins are avoided in treatment. The prognosis of fusariosis is directly related to the immune status of the patient, with high mortality rates in patients with severe and persistent neutropenia. Given the poor outcome of fusariosis, preventing infection is one of the cornerstones of management.

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Abbreviations

BAL	bronchoalveolar lavage
BDG	1→3 β-D-Glucan
CT	computed tomography
FSSC	*Fusarium solani* species complex
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
MALDI-TOF	matrix-assisted laser desorption ionization-time of flight
MIC	minimum inhibitory concentration
PCR	polymerase chain reaction
TEF	translation elongation factor

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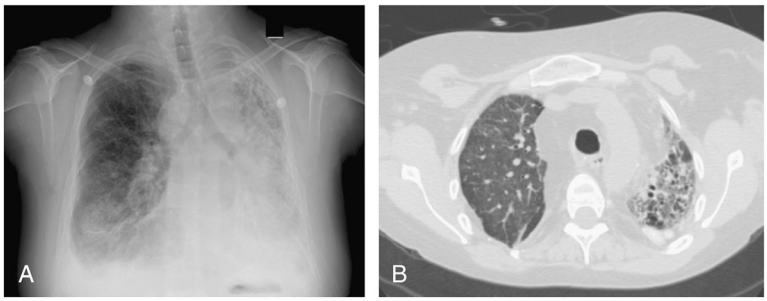

FIGURE 1.

Radiologic images of Patient 6 from this case study, with *Fusarium proliferatum, Aspergillus* species, and *Nocardia asteroides* isolated from sputum samples: **A,** Anteroposterior chest radiograph showing focal consolidation in the mid- to lower right lung likely representing pneumonia following a right thoracotomy and right lung transplantation. There are small bilateral pleural effusions, and left hemithoracic volume loss and interstitial fibrosis or traction bronchiectasis of native left lung. **B,** Axial CT scan without contrast showing fibrosis in the native left lung as evidenced by the honeycombing architectural distortion. The lower lobes demonstrate ground glass opacity and consolidation. The right transplant lung demonstrates diffuse ground glass opacity and focal consolidation with associated centrilobular nodularity.

TABLE 1

Clinical Features of 6 Cases of Fusarium Infection in Lung Transplant Patients at Massachusetts General Hospital

Patient (Age in yr/Sex)	Reason for Lung Transplant	Positive Culture Specimen	Immunosuppression at Diagnosis	Signs and Symptoms	Fusarium Treatment	Outcome	Reason for Death	Acute Rejection 6 mo Before Infection	Antifungal Prophylaxis or Previous Therapy	1Y3 B-D Glucan	Galactomannan Antigen
1 (20/F)	Cystic fibrosis	BAL	Tacrolimus, prednisone	SOB, fever, abdominal distention, PE, postural hypotension, crackles in left chest (WBC 19.2, %PMN 89, ANC 17,100)	Liposomal amphotericin B, caspofungin	Died	Invasive aspergillosis	Yes	No	ND	ND
2 (55/M)	Alpha-1 antitrypsin deficiency	BAL	Cyclosporine, azathioprine, antithymocyte globulin (ATG), prednisone	SOB, fever (97.9-F), pneumonia, hemoptysis, fine crackles on auscultation, diminished BS at base (WBC 7.1, %PMN 75, ANC 6270)	None	Died	Sepsis, ARF, scedosporium infection	No	No	ND	ND
3 (59/F)	Interstitial pulmonary fibrosis	Blood, BAL	Tacrolimus, prednisone	SOB, fever, nonproductive cough, ARF, intubated, hypoxia, fine crackles (WBC 3.9, %PMN 94, ANC 3660)	Liposomal amphotericin B, voriconazole	Died	Sepsis, *Fusarium* infection, CMV pneumonitis	No	Voriconazole, caspofungin	53	0.09
4 (66/F)	Chronic obstructive airways disease	BAL	Antithymocyte globulin (ATG), prednisone	Fever (98.1-F), hypoxia, dimished BS, otherwise asymptomatic (WBC 14.5, %PMN ND, ANC ND)	Amphotericin B, voriconazole	Survived	—	No	Fluconazole	ND	ND
5 (19/F)	Cystic fibrosis	BAL	Cyclosporine, prednisone	SOB, fever (100.3-F), hypoxia, diminished BS on affected side, no cervical lymphadenopathy, fatigue, headache, dry heaves (WBC 4.9, %PMN 78, ANC 3850)	Voriconazole	Died	Unknown	Yes	No	31	0.206

Patient (Age in yr/Sex)	Reason for Lung Transplant	Positive Culture Specimen	Immunosuppression at Diagnosis	Signs and Symptoms	Fusarium Treatment	Outcome	Reason for Death	Acute Rejection 6 mo Before Infection	Antifungal Prophylaxis or Previous Therapy	1Y3 B-D Glucan	Galactomannan Antigen
6 (36/F)	Interstitial pulmonary fibrosis	Sputum	Cyclosporine, prednisone	SOB, fever (99.5-F), chills, hypoxia, nonproductive cough, headache, coarse crackles on affected side, expiratory wheezing (WBC 8, %PMN 86, ANC 7610)	Liposomal amphotericin B, voriconazole	Died	Respiratory distress, sepsis	No	Itraconazole	ND	0.59

Abbrevations: ANC = absolute neutrophil count, ARF = acute respiratory failure, BS = breath sounds, CMV = cytomegalovirus, ND = no data, PE = pulmonary embolism, PMN = polymorphonuclear cells (granulocytes), SOB = shortness of breath, WBC = white blood cell count, 10^6cells/mL.

TABLE 2

Laboratory Features of 6 Cases of *Fusarium* Infection in Lung Transplant Patients at Massachusetts General Hospital

Patient	Reason for Lung Transplant	Positive Culture Specimen	Previous Fungal Infections	Cultured Fusarium	Fungal Stain and Microscopy	Concomitant Infection at Diagnosis
1	Cystic fibrosis	BAL	*Candida albicans, C. glabrata, Aspergillus fumigatus*	*Fusarium* spp ND	Positive (septated hyphae)	*Aspergillus fumigatus, Pseudomonas aeruginosa*
2	Alpha-1 antitrypsin deficiency	BAL	None	*Fusarium* spp ND	Negative	*C. albicans, Acinetobacter baumanni*
3	Interstitial pulmonary fibrosis	Blood, BAL	None	*Fusarium* spp ND	Positive (septated hyphae)	CMV infection
4	Chronic obstructive airways disease	BAL	*C. albicans, Alternaria* spp, Non-albicans yeast, *Penicillium* spp	*Fusarium* spp 1 colony	Negative	*Chryseobacterium (Flavobacterium) meningosepticum,* Nonenteric gram-negative rods, *Stenotrophomonas maltophilia, Alcaligenes xylosoxidans, Corynebacterium* spp, *C. albicans, Alternaria* spp
5	Cystic fibrosis	BAL	*Aspergillus versicolor*	*Fusarium* spp ND	Negative	*Pseudomonas aeruginosa* (2 types)
6	Interstitial pulmonary fibrosis	Sputum	*Mycobacterium avian intracellulare, Stenotrophomonas*	*F. proliferatum* 2 colonies	NA	*Nocardia asteroides, Aspergillus* spp

Abbrevations: ND = not determined, NA = not available.

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TABLE 3

Features of 3 Cases of *Fusarium* Infection in Lung Transplant Patients, Previous Reports

Reference (Age in yr/ Sex)	Reason for Lung Transplant	Positive Culture Specimen	Immunosuppression at Diagnosis	Signs and Symptoms	Fusarium Treatment	Outcome	Reason for Death	Antifungal Prophylaxis or Previous Therapy	Fusarium Isolate
9 (53/M)	Advanced bullous emphysema	BAL	Prednisone, azathioprine, cyclosporine	Productive cough, pleuritic chest pain, low-grade fever (98.6 -F) (WBC 7.4)	Amphotericin B	Alive after 1 yr	NA	Co-trimazole	*F. solani*
35 (18/F)	Cystic fibrosis	Central venous catheter blood cultures, BAL	Prednisone, azathioprine, cyclosporine	Apyrexial, vegetation on tricupsid valve (WBC 7.7, 75% neutrophils)	Liposomal amphotericin B	Died	Convulsion crisis, septic shock	No	*F. solani*
41 (63/M)	Emphysema (>1-antitrypsin deficiency and tobacco use)	Sputum	Prednisone, azathioprine (changed to mycophenlate mofetil), cyclosporine	Mild fever, asthenia, weight loss, productive cough, SOB (WBC 3.8, ANC 2430)	Pozaconazole	Survived	NA	Itraconazole	*F. proliferatum*

Abbrevations: See previous tables.

TABLE 4

Antifungal Susceptibilities of Fusarium Species, Previous and Present Reports

		MIC (*K*g/mL)						
Species	**Reference**	**Amphotericin B**	**Flucytosine**	**Itraconazole**	**Fluconazole**	**Ketoconazole**	**Posaconazole**	**Caspofungin**
F. solani	9	2	>64	>64	ND	ND	ND	ND
F. prolifertarum	41	2	ND	>8	>64	ND	4	ND
F. prolifertarum	PR	4	>128	>128	>128	32	ND	128

Abbreviations: See Table 1. PR = present report.