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[Article]

Fungal Infections in Lung and Heart-Lung Transplant Recipients: Report of 9 Cases and Review of the Literature

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Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; BAL, bronchoalveolar lavage; CT, computed tomography; MIC, minimum inhibitory concentration; POD, post-operative day.

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Outline

Introduction

Lung transplantation is now a therapeutic option for many end-stage parenchymal, bronchial, and vascular pulmonary diseases [11,75]. The number of transplants performed each year and the number of centers performing this procedure continue to increase. Advances in surgical techniques and immunosuppressive regimens have markedly improved the quality of life and survival of patients after transplantation [91]. However infection and rejection remain 2 major problems in the posttransplant period [91]. A balance between the 2 should be maintained at all times. Any intervention that decreases the rate of rejection, which is usually achieved by administering more immunosuppressive medications, leads to an increase in the incidence of infections. On the other hand, attempts to decrease the incidence of infections by reducing immunosuppressive medications lead to a higher incidence of rejection. Although bacterial and viral organisms cause the majority of infections after lung transplantation, fungal infections are associated with the highest morbidity and mortality [19,25,34]. Most fungal infections in these patients are caused by Candida and Aspergillus species. On the other hand, as our experience with transplants increases, other primary pulmonary pathogens such as Histoplasma capsulatum and Cryptococcus neoformans and unusual opportunistic fungal pathogens will occur [51,91]. While the respiratory tract is an obvious portal of entry in these patients, the gastrointestinal tract and intravascular catheters may also be sources for fungal infection [51]. Also, unique to this population, donor organs can be reservoirs for pathogenic fungi, which may have been dormant in or insignificant to the donor but can be a source of posttransplantation fungal infection in the immunosuppressed recipient [77,86]. Recipients of lung transplantation may be particularly susceptible to respiratory tract infections with yeasts and molds, as the lung is the only transplanted organ that has continuous contact with the external environment with its myriad of yeasts and spores.

We reviewed our experience with fungal infections in patients undergoing lung and heart-lung transplantation at Duke University Medical Center from September 1992 until July 1995. Herein we describe 9 cases and report on the other fungal infections encountered during this time period. We identify and illustrate a variety of factors in pathogenesis, epidemiology, and management that are unique to fungal infections in lung transplant recipients.

Case Reports

Case 1: Candida pneumonia resulting in disseminated disease

A 45-year-old woman with a history of Eisenmenger syndrome underwent bilateral lung transplant on June 14, 1995. Her postoperative course was complicated by profound respiratory failure and she was placed on extra corporeal membrane oxygenation. Perioperatively she received ceftazidime, vancomycin, trimethoprim-sulfamethoxazole, and ganciclovir. A pretransplant biopsy from the donor lung showed no significant edema or inflammation. Because of worsening respiratory status the patient was reexplored on postoperative day (POD) 5 and found to have a necrotic left lower lung. Pathology revealed severe pulmonary hemorrhage and focal necrosis in the left lung without evidence of rejection. Culture of lung tissue grew Candida albicans. Fluconazole was started at 400 mg for 1 dose, then 200 mg/day. On POD 11, because of fever and continued poor oxygenation, she underwent a repeat bronchoscopy and biopsy. The bronchoalveolar lavage (BAL) specimen showed white blood cells with rare yeast. A transbronchial biopsy from the left lung showed fibrinopurulent material with a fungus ball of yeast forms and pseudohyphae consistent with candida Figure 1. Also blood, sputum, BAL and

peritoneal fluid from POD 14 grew Candida albicans. Because of persistent fever and no apparent response to fluconazole after 7 days of treatment, the patient was switched to amphotericin B at 0.5 mg/kg per day. On POD 23, the patient was found to have brownish drainage from the lateral aspect of the left thoracic wound. Upon exploration a necrotic rib was found. Extensive debridement was done and pathology revealed granulation tissue with microabscesses. KOH stain showed budding yeast with pseudohyphae. Cultures of blood, skin, and the rib specimens all grew Candida albicans. Five days later a computed tomography (CT) scan of the abdomen showed a large amount of free intraperitoneal fluid with a small fluid collection anterior to the liver, which was drained under CT guidance. The KOH smear showed pseudohyphae and yeast. The patient had received 600 mg of amphotericin B at the time of this finding. A transesophageal echocardiogram revealed no vegetation. The amphotericin B dose was increased to 0.8 mg/kg per day and flucytosine at 37.5 mg/kg 4 times a day was started. The minimum inhibitory concentration (MIC) of the Candida albicans from the BAL to fluconazole on POD 21 was more than 64 mu g/mL and from the lung biopsy obtained on POD 5 was 8 mu g/mL, by macrobroth susceptibility testing using the National Committee for Clinical Laboratory Standards criteria [82]. Karyotyping studies using pulsed field gel electrophoresis identified that the Candida albicans isolated from the lung tissue 2 days after transplant had the same chromosome pattern as the ones grown subsequently from the blood, the peritoneal fluid, and the hepatic fluid collections. Repeat blood cultures on POD 34 grew Candida albicans. The patient continued to do poorly with episodes of hypotension, fever, and hypothermia and died with a pseudomonas bacteremia. The total dosage of amphotericin B the patient received was 936 mg.

Comment:

Candida species are the most common cause of fungal infections in heart-lung and lung transplant patients [91]. The clinical pattern ranges from mucocutaneous to invasive disease. In many seriously ill patients on antibiotics, isolation of candida from sputum is very common but pneumonia is considered unusual [19]. Lung transplant recipients also have a high incidence of candidal colonization of the trachea and the bronchial secretions [91]. Brooks et al [19] reported 1 case of invasive candida pneumonia involving both lungs diagnosed at autopsy in a lung transplant patient who repeatedly grew candida from premortem sputum and BAL samples. Another patient had autopsy-proved invasive candida tracheitis. Although candida pneumonia is uncommon in other clinical conditions except prolonged neutropenia [74,109], our case illustrates the rapidity and severity of this disease in lung transplant patients. The isolation of candida from a patient with pulmonary infiltrates after lung transplantation should not be dismissed as only colonization, and early histopathologic confirmation is essential for the diagnosis and the institution of aggressive antifungal therapy. In vitro susceptibility testing for fungi has only shown in vitro-in vivo correlation with thrush in patients with the acquired immunodeficiency syndrome (AIDS). In this patient fluconazole MICs of Candida albicans rose to high levels after exposure to fluconazole. Until more data are available, the need to test serial candida isolates for in vitro susceptibility to antifungal drugs in this severely immunocompromised population remains controversial, but drug resistance may be a reason for treatment failure.

Case 2: Disseminated Candida albicans originating from the donor lung

A 34-year-old woman with history of primary pulmonary hypertension underwent bilateral lung transplant on April 25, 1995. The donor was a healthy 33-year-old male, victim of a motor

vehicle crash, who spent 1 day in an intensive care unit (ICU) at another hospital prior to death. Donor specimens obtained from the right lung had yeasts and pseudohyphae on KOH stain and grew Candida albicans. One specimen had Aspergillus glaucus and Penicillium species in addition to the Candida albicans. The patient's immediate postoperative course was complicated by fever, leukocytosis, and bilateral diffuse pulmonary infiltrates. On POD 5 she had a cardiopulmonary arrest, requiring direct cardiac massage. She underwent a bronchoscopy. The BAL culture grew Candida albicans. The patient had persistent fever and leukocytosis despite treatment with ceftazidime and vancomycin. Intravenous fluconazole was started on POD 7 at 800 mg per day. Subsequent blood and peritoneal fluid cultures grew C. albicans. Fluconazole was stopped and intravenous amphotericin B at 0.5 mg/kg per day was started. The patient also received 15 mg of amphotericin B intraperitoneally every other day for 10 days. She received a total of 1 g of intravenous amphotericin B, and all subsequent cultures sent from blood, BAL, and endotracheal secretions were negative for fungi. Her course was further complicated by recurrent Gram-negative bacteremia with Burkholderia cepacia leading to her death. The C. albicans isolates from the donor lung prior to transplant, the patient's transplanted lung, the blood, and the peritoneal fluid after transplantation were all identical by karyotypic analysis.

Comment:

Most cases of candidiasis in immunocompromised patients are considered to originate from endogenous sources such as the gastrointestinal tract, or exogenous sources through intravenous lines or urinary catheters. Using karyotyping as an epidemiologic tool, this case illustrates that the donor lung can be a source of fungal infection in the recipient. Donor organs have been described to transmit pathogenic fungi such as Cryptococcus neoformans [86]. Most donor organs are probably contaminated with candida species secondary to unsuspected candidemia associated with terminal care with antibiotics and respirators. The donor in this case was a healthy adult who had spent only 1 day in the intensive care unit. This case shows that the donor lung can be colonized shortly after intubation and may be a source for rapidly evolving pneumonia in the heavily immunosuppressed recipient. The use of donor lung cultures to evaluate the risk of fungal pneumonia remains unclear, however. Although the yeast in the donor lung caused infection, 2 other isolated molds from the donor lung (aspergillus and penicillium), apparently were not important in the patient's infection. The clinical use of these donor cultures for fungi should be studied carefully for importance, or the problem could be obviated by the use of prophylactic antifungal agents.

Case 3: Infection with Candida albicans causing necrosis of the anastomosis

A 42-year-old woman with chronic obstructive pulmonary disease received bilateral lung transplantation on June 23, 1995. She had an uncomplicated immediate postoperative course and was discharged home after 8 days. Three days later she was readmitted for progressive dyspnea on exertion and bilateral pulmonary infiltrates on chest radiograph. Bronchoscopy revealed stenotic anastomoses with erythematous mucosa and a dark necrotic appearance. The endobronchial biopsy showed coagulation necrosis with fungal forms consistent with pseudohyphae and yeast Figure 2. The BAL cultures grew Candida albicans. The patient was started on intravenous amphotericin B at 0.5 mg/kg per day. In addition 50 mg of amphotericin B in 5 cc of H_2 O was given in a nebulized form daily for 14 days, because of the concern that the dose of systemic amphotericin B might not penetrate the area of necrosis. Ten days later, because of worsening renal function, amphotericin B was stopped and the patient was started on

fluconazole at 200 mg per day. The total intravenous amphotericin dosage received was 275 mg. The patient was discharged home on fluconazole and once-weekly nebulized amphotericin B with a stable outpatient course. She remained on treatment for 4 months. Follow-up bronchoscopy showed resolution of the initial findings.

Comment:

Lung transplant recipients are often colonized with candida (86%) [19] and aspergillus (25%), [66] which may affect healing of the bronchial anastomosis [54]. The anastomotic site is particularly vulnerable because of the poor blood supply and the presence of suture material that initiates a local immune response [64]. Fungal tracheobronchitis has been well described [10,21,64,85,93,96,120]. Invasive bronchial fungal infection after lung transplantation has also been reported [13,64]. Kramer et al [64] described ulcerative tracheobronchitis after lung transplantation caused by Aspergillus species. These patients had either multiple ulcers covered with necrotic material, severe tracheobronchitis with erythematous edematous mucosa, or pseudomembrane formation. The 3 patterns were felt to represent the progressive spectrum of the disease. In all patients, endobronchial biopsies showed necrotic cartilage invaded by large amounts of fungal organisms, whereas transbronchial biopsies did not show evidence of parenchymal disease. All patients who were treated with itraconazole showed resolution of the inflammation, disappearance of the ulcers, and negative cultures after 4-12 weeks. Two patients who were not continued on itraconazole because of either intolerance or malabsorption died of disseminated aspergillosis. These results suggest that itraconazole can penetrate into tracheobronchial secretions. Our patient responded very well to a combination of systemic antifungals, amphotericin B and fluconazole, and inhaled amphotericin B. Whether the latter modality added to the successful treatment is unknown, since inhaled amphotericin B has not been studied in the treatment of such conditions in humans. However the necrosis associated with poor blood supply around the anastomosis makes topical therapy an attractive way to deliver this drug. Topical amphotericin B delivery has been reported to be effective in the prophylaxis of fungal infection in animals and humans [2,22,50,56,70,80,114] and in the treatment of fungal infections in mice [41,42] but needs to be studied prospectively in the treatment of such conditions in humans.

Case 4: Subclinical aspergillus infection detected early after transplantation and treated with itraconazole

A 45-year-old man with a history of primary pulmonary hypertension underwent bilateral lung transplantation on March 16, 1995. His immediate postoperative course was uncomplicated and he was discharged home 11 days posttransplant. Over the next month, he noted gradual decrease in exercise tolerance with shortness of breath and diaphoresis on minimal exertion. He developed a daily cough with brownish sputum production but without fever. Chest radiograph revealed persistent right pleural effusion with left basilar atelectasis, since the postoperative period. Bronchoscopy and transbronchial biopsy revealed focal collection of loose fibrin and neutrophils in 1 fragment of alveolar lung tissue. Special stains demonstrated rare and fragmented hyphal forms. The BAL grew Aspergillus fumigatus Figure 3A. The patient was admitted and started on amphotericin B. After treatment for 5 days at 40 mg/day, his serum creatinine increased. Amphotericin B was discontinued and he was started on itraconazole at 400 mg/day. Serum itraconazole level was 7.8 mu g/mL. The patient's symptoms improved and he was discharged home on itraconazole. Repeat bronchoscopy 10 days later revealed bilateral

bronchial stenosis. The patient underwent a successful balloon dilatation of the right main stem bronchus, and debris were suctioned from the left main bronchus, which achieved patency. Transbronchial biopsy revealed acute inflammation and necrosis. Methenamine silver and periodic acid-Schiff stains revealed yeast forms with pseudohyphae seen within the granulation tissue and necrotic lung tissue and cartilage Figure 3B. Fungal cultures from lung tissue grew Candida tropicalis. The patient remained on 400 mg of itraconazole for 4 months, and repeat bronchoscopies were unremarkable. At 7 months follow-up the patient remains stable.

Comment:

The prognosis of invasive aspergillus infection is poor, with a mortality rate exceeding 90% in some patient populations [28]. However, prompt diagnosis and early therapy may improve the outcome [1,62]. Invasive aspergillus infection has been reported to occur in 15%-18% of heart-lung and lung transplant patients [46,64]. The manifestations may range from tracheobronchitis to lung parenchymal involvement and disseminated disease. Although colonization is common in these patients (32%) [38], the presence of a positive culture from a lung transplant patient with necrotic airways or radiographic abnormalities should raise the suspicion of invasive disease and lead to an aggressive workup including tissue biopsies [20]. Amphotericin B has been the mainstay of treatment for invasive aspergillosis [28], but its use can be associated with significant toxicity in solid organ transplant patients on cyclosporine [59,61], and alternative options are needed. Itraconazole has been studied for treatment of humans and animals with invasive mycoses [27,29,35,37,43,88,94,123]. In a recent open-label trial, itraconazole was found to have significant efficacy in invasive aspergillosis [27]. Failure rates were lower in pulmonary disease and in solid organ transplant. Our case illustrates the good outcome of invasive aspergillosis after lung transplantation when it is diagnosed early and treated promptly. Itraconazole should be considered after initial treatment with amphotericin B in patients with a slowly progressive course and in those who cannot tolerate amphotericin B, but it is essential to document oral absorption of the drug. The optimal peak drug level of itraconazole is not certain, but we would be encouraged by levels over 5 mu g/mL. Because of the long half-life of itraconazole, the time of the blood levels is of little importance. Itraconazole should be taken with food for better bioavailability [8]. Clinicians should also be aware of possible interaction between itraconazole and H_2 receptor antagonists, leading to poor absorption of itraconazole, and therefore should monitor serum itraconazole concentrations carefully in seriously ill patients [27].

Case 5: Disseminated aspergillosis occurring in a patient with mycetomas in the native lungs who was maintained after transplant on antifungal prophylaxis

A 42-year-old man with end-stage sarcoidosis involving the heart and the lungs, with mycetomas documented by chest radiograph and CT scan of the lungs, underwent a heart-lung transplantation on February 18, 1995. Pathology of the native lungs revealed end-stage sarcoidosis with bilateral pulmonary mycetomas. The patient was treated with ceftazidime, vancomycin, and acyclovir, and because of the mycetomas, antifungal prophylaxis was deemed appropriate. On the day of transplantation he received a 35 mg dose of intravenous amphotericin B. His immediate postoperative course was complicated by acute tubular necrosis with anuria. He was started on hemodialysis and amphotericin B was discontinued. Instead, he was placed on daily itraconazole at 400 mg administered through a nasogastric tube. The native lung culture grew Aspergillus fumigatus. Because of the concern over absorption of itraconazole, a blood

level was checked and was found to be less than 0.5 mu g/mL. Itraconazole was discontinued and liposomal amphotericin B (Ambisome) was started at 5 mg/kg every other day. Because the BAL from the third day after transplantation was reported to grow Aspergillus fumigatus 10 days later, the liposomal amphotericin B dose was changed to 5 mg/kg daily. On POD 22, his white blood cell and platelet counts started to drop. The total liposomal amphotericin B dosage received at that point was 3.74 grams. Frequent bronchoscopies showed the anastomosis to be intact, but the mucosa progressively became more erythematous and friable. The patient developed altered mental status. Head, abdominal, and chest CT scans and a lumbar puncture results were all unrevealing. He progressed to death, and BAL fluid from 1 day premortem grew Aspergillus fumigatus.

Autopsy was limited to the heart and lungs. Microscopic examination revealed invasive aspergillus involving the epicardium, myocardium, endocardium. and coronary vasculature. A thrombus seen in the left anterior descending artery contained numerous septated hyphal forms. In other vessels the fungus was seen invading the walls. Collections of hyphae were present in areas of myocardial necrosis and adjacent areas where the myocardium was more viable. Representative segments of the right and left lungs showed pleural nodules containing branching hyphae consistent with aspergillus Figure 4. Collections of organisms were present in the lung parenchyma with invasion into blood vessels and alveolar septae.

Comment:

This case illustrates the difficulty in controlling aspergillus infection in immunocompromised patients despite antifungal therapy. Liposomal amphotericin B has been shown to preserve the in vivo [44] and in vitro [6,98] activity of amphotericin B, although it is uncertain what is the most effective dose for liposomal amphotericin B in the treatment of aspergillosis. The absorption of itraconazole is known to be erratic and a concern in this patient population; our patient was without adequate antifungal coverage for several days after transplantation, as documented by undetectable drug levels. This patient developed aggressive disseminated aspergillosis early after transplantation. Patients with mycetomas are likely to be at high risk to develop disseminated fungal infection after immunosuppressive therapy. It is conceivable that long-term antifungal prophylaxis pretransplant may decrease the fungal burden which could be quite high at the time of transplantation and lead to an improved outcome; however, this remains to be proved. If itraconazole is used, serum levels should be monitored to ascertain adequate absorption [29,90]. Inhaled amphotericin B is an alternative way to deliver antifungal prophylaxis to these patients. Its use in this form has not been associated with any significant side effects, and high concentrations of drug can be delivered within the lungs [2,22,50,56,70,80,114]. Because of the risk of disseminated aspergillosis once on immunosuppressive therapy, patients with pulmonary mycetomas are less than ideal candidates for lung transplant, and strategies should be employed to reduce the fungal burden prior to transplantation.

Case 6: Cryptococcus neoformans infection occurring early posttransplant

A 24-year-old woman with primary pulmonary hypertension underwent bilateral lung transplant on May 11, 1995. She was treated perioperatively with ceftazidime, vancomycin, and ganciclovir. On histology, donor lungs showed small airways disease with occasional fibrin thrombi. Focal lymphoid infiltrate with recent hemorrhage were present in the native lung. A perfusion scan done after the transplantation revealed no flow to the left lung. Revision of the left pulmonary

artery anastomosis restored the flow to the lung. On POD 2 the patient became febrile with leukocytosis and significant hypoxemia. Chest radiograph showed left lower lobe air space disease. Endotracheal suction cultures from POD 2 were reported on POD 7 to grow Cryptococcus neoformans and Penicillium species. The patient was started on 400 mg of fluconazole daily. The donor lung cultures prior to implantation grew rhodotorula. Serum cryptococcal antigen was negative, as were blood cultures. Repeat bronchoscopy on the fourth postoperative day showed significant airway inflammation with purulent BAL washings. Repeat BAL fluid fungal cultures on POD 12 were negative. Transbronchial biopsy of the right lower lobe showed lymphocytic bronchitis with scattered eosinophils. The patient was discharged home on fluconazole. She received 4 months of treatment and has remained stable on close follow-up.

Comment:

Cryptococcal infection is generally acquired by inhalation [26,51]. The isolation of this organism from the sputum is generally associated with disease but can represent colonization. Occasionally, Cryptococcus neoformans is recovered from sputum of patients with chronic obstructive or restrictive lung disease without any infiltrates or clinical symptoms [26]. Cryptococcal infection is the third most common fungal infection in solid organ transplant [51,91], but the disease is notably absent during the first 4-6 months after transplantation [51]. The occurrence of such infection during this early posttransplant time period would suggest an unusually intense environmental exposure. However, donor organs are also potential sources of posttransplantation pathogens. In canine lung recipients, bacterial contamination of the donor lung leads to pneumonia in the recipient [33]. In humans, transfer of viral [12,91], bacterial [32,54], fungal [86], and protozoal [47,112,119] organisms in donor organs has been documented in other transplant populations. This would appear to be a potentially serious problem in lung transplant recipients because the lungs are known to be a reservoir for primary fungal pathogens and mycobacteria [19]. This mode of transmission has not been reported in recipients of lung transplantation, however, except in the case of bacterial pathogens [54]. The cases of cryptococcal infection reported after lung transplantation were thought to be related to inhalation of the organisms after surgery [91]. Since our patient had the yeast grown 2 days after transplantation, while still in the intensive care unit, we believe that the organism was transmitted by the donor organ despite the initial negative donor lung cultures. Because the patient was immunosuppressed, we elected treatment to prevent disseminated disease [60]. Standard therapy for serious cryptococcal infections has long been amphotericin B with or without flucytosine [9]. However, because of significant nephrotoxicity related to the interaction of amphotericin B and cyclosporine [59], fluconazole therapy was considered in this patient who was not acutely ill. Fluconazole has been used successfully for the treatment of invasive fungal infections in organ transplant recipients [23] and in the treatment of cryptococcal meningitis in patients with AIDS [113].

Case 7: Pneumonia with Cryptococcus neoformans occurring 6 months posttransplant

A 58-year-old woman with a past medical history significant for emphysema and allergic reactions to penicillin and sulfa drugs underwent right single lung transplantation on November 8, 1994. Pretransplant skin testing with intradermal antigens showed a 2-mm reaction to histoplasma at 72 hrs, with no reaction to mumps. Her immediate postoperative course was uneventful and she was discharged home 1 week later. Six months posttransplant, she presented complaining of right-sided pleuritic chest pain and occasional dry cough, decreased exercise

tolerance over 1 month, without fever, chills, or night sweats. Chest radiographs revealed air space disease in the right upper lobe. Bronchoscopy was unremarkable and transbronchial biopsies revealed moderate rejection. Due to the clinical presentation, it was felt that a larger section of tissue was needed to rule out infection before increasing her immunosuppressive therapy. The patient underwent a thoracoscopic biopsy of the right upper lobe which showed organizing pneumonia. Special stains showed fungal forms compatible in size with Histoplasma capsulatum, less likely to be torulopsis or a small unencapsulated cryptococcus. Repeat radiographs showed progressive opacification. Because of renal insufficiency, amphotericin B was not considered and instead, the patient was started on itraconazole at 400 mg per day. Four days later a maculopapular rash was noted involving the trunk and extremities. The lung biopsy was then reported to grow Cryptococcus neoformans. Itraconazole was stopped and the patient was started on 400 mg of daily fluconazole, after she had a negative lumbar puncture. The rash continued to worsen for 2 days and became more pruritic, so fluconazole was held. It was restarted 2 days later, after the rash had disappeared. The patient tolerated the reinstitution of fluconazole without adverse events. She was discharged home and has remained stable with marked improvement in her symptoms. At 10 months follow-up she remained asymptomatic.

Comment:

This case represents the usual period, 6 months posttransplantation, for the occurrence of cryptococcal pneumonia [51]. Because of the size of the yeast (2-4.5 micro meter), it was initially mistaken for histoplasma, and special stains (mucicarmine, Alcian blue) for capsule were not helpful. Thus, this organism in vivo was hypocapsular and therefore confused the pathologist who felt that the histology was consistent with histoplasma. Correct differentiation between the 2 organisms required culture confirmation in this case. Since cryptococcal pneumonia can be associated with subclinical meningitis at the time of presentation [26,111], it is important to diagnose correctly the extent of this infection, and a lumbar puncture ruled out central nervous system disease. This case also illustrates that cross-drug reaction between the 2 different triazole compounds, itraconazole and fluconazole, does not always occur.

Case 8: Histoplasma capsulatum isolated from a surveillance bronchoscopy 1 week after lung transplantation in an asymptomatic patient

A 60-year-old man with severe chronic obstructive pulmonary disease underwent a left single lung transplant on November 11, 1994. On POD 15, he developed fever with mild hypoxemia. Bronchoscopy revealed a patent anastomosis with slight erythema of the mucosa. Cultures were initially reported to be negative. The patient was treated with 3 doses of 500 mg of methylprednisolone for presumed rejection with improvement in oxygen saturation, exercise tolerance, and fever. On December 19, 1994, the BAL fluid fungal culture from November 26, 1994, was reported to show growth of Histoplasma capsulatum. A repeat bronchoscopy was done on December 21, 1994. BAL fluid fungal cultures also grew Histoplasma capsulatum. At that time, the patient was asymptomatic. Liver function tests and blood counts were normal except for mild leukopenia. The chest radiograph showed no air space disease. He was started on 400 mg of itraconazole per day. Subsequently, surveillance fungal cultures from BAL obtained at months 3, 6, 9, and 12 posttransplant and held for 8 weeks were negative. He remains on itraconazole. The patient was born and grew up in North Carolina where he currently resides, but he traveled to the Mississippi and Ohio River valley areas many years ago when he was in the military.

Comment:

This patient had no evidence of previous infection with histoplasma as documented by skin testing or evidence of old granulomatous disease on radiograph prior to transplant. The donor lung did not grow histoplasma but the culture was not plated on fungal media with prolonged incubation. The patient had his first positive culture for histoplasma 15 days after transplant, before he had left the hospital, which makes environmental exposure very unlikely. Since the patient underwent single lung transplantation it is conceivable that he had been infected with histoplasma in the past and had reactivation of the infection on immunosuppressive therapy. An alternative explanation is that the donor lung transmitted the infection. Disseminated and pulmonary histoplasma in organ transplant patients have been well described [51]. Patients living in endemic regions tend to develop primary disease, while patients living in nonendemic areas present with reactivated infection. Reports of histoplasma infection on lung transplant recipients are few. This case is unusual because the fungus was cultured at a time when the patient was asymptomatic. However, it emphasizes the importance of surveillance cultures for fungi in these patients. We suspect that early administration of antifungal therapy in this patient prevented a serious disseminated case of histoplasma.

Case 9: Pityrosporum folliculitis in lung transplant patients

A 26-year-old man with cystic fibrosis had multiple episodes of infections with resistant Xanthomonas maltophilia and Burkholderia gladioli. He underwent bilateral lung transplant on August 3, 1995. His immediate postoperative course was complicated by fever and hypotension. Blood cultures grew Burkholderia gladioli only sensitive to piperacillin and ciprofloxacin. The patient had been maintained on propofol for sedation and was started on enteral tube feeding. Five days after transplantation, he developed pustules on his chest, trunk, and neck Figure 5 together with high-grade fever. One of the pustules was unroofed and KOH revealed multiple budding yeasts. Skin biopsy showed similar organisms located exclusively within intact and ruptured hair follicles Figure 6. His central venous catheter was pulled, propofol was stopped, and intravenous fluconazole was started at 200 mg for 1 dose followed by 100 mg daily. Blood cultures were negative, and skin culture plated with oil supplementation grew Malassezia furfur (pityrosporum). The patient received 7 days of fluconazole. The rash resolved and he quickly defervesced.

Comment:

Two other lung transplant recipients at Duke had similar presentations with fever and a follicular rash in the same distribution; both were initially thought to have disseminated fungal infection when the unroofed lesions showed budding yeasts. Because these patients were on broad spectrum antibiotics, had central venous lines, were receiving total parenteral nutrition, and were on high doses of immunosuppressive therapy including steroids, disseminated candidiasis was a major concern, and patients were started on amphotericin B. Both patients had skin biopsies showing budding yeasts only within hair follicles, without involvement of the dermis. The fungal cultures remained negative. Because of the structure and the location of the yeast, and the fact that the fungus did not grow on media that was not supplemented with oil, malassezia infection was suspected. Amphotericin B was discontinued, and both patients responded to discontinuation of the central lines and the parenteral nutrition and treatment for 5 days with intravenous fluconazole. Because the patient described in case 9 was also receiving

propofol, a lipid-based drug, malassezia was suspected, which led us to use oil in culturing the skin biopsy.

Malassezia is widely distributed on normal skin, especially the trunk, face, and scalp [107]. Leeming et al [68] reported that 100% of 16 healthy adults were colonized with M. furfur. Under high temperature and high relative humidity, malassezia produces hyphae and leads to tinea versicolor [73]. The incidence of tinea versicolor is higher in immunocompromised patients than in immunocompetent hosts. In 1 study of 200 consecutive renal transplant patients, it was documented in 18% of the patients [63]. Under certain conditions, malassezia causes severe folliculitis presenting as erythematous papules or pustules located predominantly over the trunk, up-per extremities, and the face [39]. Most of the lesions are located around hair follicles. Recently, data from several institutions have also implicated M. furfur as causing a number of more invasive infections, including intravascular catheter-associated sepsis [3,18,24,40,100,117], and pulmonary infections [102]. Malassezia folliculitis usually responds to topical azole compounds and does not require systemic amphotericin B. This condition should not be confused with disseminated candidiasis, which requires aggressive systemic antifungal treatment. Since blood cultures are only positive in 25%-50% of cases of disseminated candidiasis [16,36], skin biopsy becomes very valuable in differentiating the 2 conditions in patients who have a papular skin rash. Physicians should be aware of this condition and must communicate to the laboratory the need to include special procedures (oil supplementation) when they suspect infection with malassezia.

Microbiology Methods

We routinely perform surveillance cultures in lung transplant recipients. Before transplantation the donor and the recipient lungs are cultured for bacteria and fungi to guide antimicrobial therapy. Following transplantation patients undergo surveillance bronchoscopies with BAL at 1, 3, 6, 9, 12, and 18 months, then yearly. BAL is sent for cytology; Gram, KOH, and acid-fast bacilli stains; and immunostains for respiratory viruses including cytomegalovirus. Also bacterial, mycobacterial, fungal, and viral cultures are performed. Fungal cultures are plated on 3 different media; the brain heart infusion agar which allows the growth of most fungi and Nocardia asteroides, the inhibitory mold agar which has gentamicin and chloramphenicol, and the inhibitory mold agar with 10% sheep blood with gentamicin, chloramphenicol, and cycloheximide. All fungal cultures are held for 4 weeks. When infection with the dimorphic fungi is suspected, cultures are held for 8 weeks. Fungal serologies are not routinely performed unless the donor or recipient are at risk for infection with the geographically restricted fungi.

Results

From September 1992 until August 1995, 59 of the 73 (81%) lung and heart-lung transplant recipients had positive fungal cultures at some point after transplantation. A number of these cultures were thought to represent colonization and therefore were not treated. Thirty percent of all patients had invasive disease as evidenced by tissue invasion detected by positive blood cultures, bone marrow cultures, or skin lesions with positive cultures or histopathology. Eighteen patients (24.6%) grew aspergillus from respiratory samples Table 1. Some patients had more than 1 Aspergillus species grown on different cultures. Three patients had invasive aspergillosis documented by histology. Three other patients had aspergillus isolated from BAL fluid during an acute respiratory illness. All 3 had no evidence of fungal invasion or cytomegalovirus infection by

transbronchial biopsy and failed to respond clinically to antibacterial therapy. These 3 patients responded clinically to antifungal therapy, and it was felt that aspergillus infection contributed to their symptoms. However, 12 (66.6%) of the patients who grew aspergillus at a screening bronchoscopy did not receive any antifungal therapy. All these patients were subsequently followed-up closely and had repeated bronchoscopies with BAL that failed to grow aspergillus. Nineteen patients (26%) had Candida species isolated from blood or body secretions, some with more than 1 species from different sites. Eight of them (42%) had invasive candida infection documented by positive blood or tissue cultures Table 2. Eleven (58%) had positive urine or BAL cultures, but these were not thought to represent invasive disease. The asymptomatic patients with candida isolated from BAL had repeated bronchoscopies with negative fungal BAL cultures. Three patients had Cryptococcus neoformans (including cases 6 and 7), and 1 patient had Histoplasma capsulatum Table 3. Three patients had folliculitis due to malassezia. The lungs were believed to be the portal of entry for all fungi except for malassezia infections. A series of molds were recovered from the lungs in BAL fluid, which may have contributed to pulmonary disease by uncertain mechanisms. We have yet to document invasive or disseminated disease with these molds, however. Sixteen of our patients (22%) grew penicillium species at different occasions. These were thought to represent contamination or colonization and therefore were not treated. Also, other filamentous fungi including dematiaceous fungi were isolated from 32 different cultures from BAL or sputum samples. Some patients had several fungi recovered at different time periods. These included a variety of isolates Table 4. These isolates were considered to represent colonization or laboratory contamination and therefore were not treated. None of the patients has had evidence of invasive disease on close follow-up.

Discussion

The success of lung transplantation has created an increasing patient population at risk for invasive and life-threatening infections [51,91]. Multiple factors explain the high frequency of fungal infections in lung transplant recipients. In addition to the drug-induced cell-mediated immunodeficiency, the alteration of ciliary action of the respiratory epithelium [31,99,116], and the dysfunction of alveolar macrophages and neutrophils [91], lung transplantation results in disrupted lymphatic and neural connections to the implanted organ, abolishing important reflexes and making it a favorable milieu for infections [52]. Inadequate blood flow to the lung also predisposes to infection in the posttransplant period [54]. Rejection episodes leading to airway inflammation increase the risk of infection particularly after treatment of the rejection episode with increasing immunosuppressive drugs [111]. Cytomegalovirus infection has also been found to be an additional risk factor for fungal infections in these patients [91,111].

In lung and heart-lung transplant recipients, the incidence of fungal infections has been reported to range between 15% and 35% [19,25,34,66]. Flume et al [38] reported an incidence of invasive fungal disease of 7% in cystic fibrosis patients and 13% in the non-cystic fibrosis population. Eight patients had invasive fungal infections, with 6 caused by candida and 2 caused by aspergillus. Forty-five of 59 patients grew Candida species, and 19 grew aspergillus. These were thought to represent colonization and therefore were not treated. Bertocchi et al [11] reported an incidence of fungal infection of 27.5% (19/69) in their lung transplant patients. Six of their patients died of invasive fungal disease: 4 with aspergillus, 1 with candida, and 1 with rhizopus. Cahill et al [20] isolated aspergillus from 69% (48/69) of their lung transplant recipients in the first year posttransplantation. Twenty-eight of the 41 (68.2%) patients who grew aspergillus once

received no antifungal therapy. Five of the 39 deaths (13%) were due to invasive fungal infections, and in 2 deaths the diagnosis was made only postmortem.

Knoop et al [62] described invasive fungal tracheobronchitis in 8% and invasive fungal pulmonary disease in 12% of their patients, for an overall incidence of 19%, responsible for 62% of the deaths. Peters et al [94] describes a rate of aspergillus infection of 14.1%; another 17% had an isolated positive respiratory culture for aspergillus without clinical correlation. Guillermain et al [46] reported an incidence of invasive aspergillosis of 18% in heart-lung and lung transplant recipients. Kramer et al [66] noted a 14% incidence of fungal infection. One-fourth of their patients grew aspergillus after transplantation, but disseminated disease was only diagnosed in 3 of them. Dummer et al [34] reported an incidence of fungal infections of 22% (5 episodes in 4 of 14 patients): 3 with invasive candidiasis, 1 with cryptococcus, and 1 with aspergillus. All 4 patients died. Brooks et al [19] evaluated the incidence of positive fungal cultures in their heart-lung transplant patients. Despite a high prevalence of positive cultures (23 respiratory and 9 urinary specimens), only 2 patients had invasive candida infection diagnosed at autopsy.

Six pathogens cause the majority of these infections in lung and heart-lung transplant recipients, including Candida albicans; Cryptococcus neoformans; the filamentous fungi, especially aspergillus; and the dimorphic geographically-restricted agents, including histoplasma, coccidioides, and blastomyces [51]. The incidence of fungal infections after lung transplantation is largely determined by the degree of immunosuppression and by epidemiologic exposure [51]. Most of the exposure, except for aspergillus, occurs prior to transplantation but the disease manifests itself after patients are started on immunosuppression. Hospital exposures to aspergillus from contaminated air conditioning systems and in areas where construction and renovation are undergoing are well described [7,53,55,69,124]. Morbidity and mortality due to these fungal infections in the lung and heart-lung transplant population is very significant. Of the different types of severe infections in this population, fungal infections have the highest morbidity and mortality [91], with overall mortality ranging between 40% and 70% [19,25,34].

Aspergillosis is the most dreaded infection because of associated high mortality despite the best available treatment options. It occurs in 14%-18% of lung and heart-lung transplant patients [46,66]. Risk factors in this patient population include immunosuppressive therapy, (especially after treatment of rejection), neutropenia, intercurrent infection with cytomegalovirus [51], hospital construction, and chemotherapy for posttransplant lymphoproliferative disorders. Preoperative colonization with asper gillus in patients with cystic fibrosis and bronchiolitis obliterans may increase the incidence of invasive aspergillosis after transplantation, but in 1 study [38] this was not found to be statistically significant. In addition to aspergillus, other emerging filamentous fungi, including fusarium and dematiaceous fungi, are potential threats in immunocompromised patients [4,5,14,30,87,101], including lung transplant patients [97]. Rabodonirina et al [97] recently reported a case of disseminated Scedosporium prolificans infection after single lung transplantation. The lung transplant recipient is unique in that the transplanted organ is directly exposed to the environment and the myriad of fungal spores. It is encouraging that we have seen so few filamentous fungal infections, although it is likely that some of these relatively less virulent fungi will cause disease in this population. We must keep a careful watch for these fungi in histopathology specimens, and we must be careful not to expose these patients to these fungi iatrogenically. Contamination of a bronchoscope with Rhinocladiella

atrovirens has been reported [17] from our institution.

Despite the high mortality associated with invasive fungal infections in lung transplant recipients, care should be taken in interpreting the results of positive cultures in asymptomatic patients. As our data show, molds and Candida species are frequently isolated from respiratory samples in the posttransplant period without any clinical significance. Careful follow-up, repeated bronchoscopies, and biopsies when indicated are recommended in these patients. The clinical diagnosis of invasive fungal infections in lung transplant patients is difficult without histopathologic support. The clinical presentation is often nonspecific, although the presence of pleuritic chest pain, hemoptysis, and nodular or cavitary infiltrates should strongly suggest the diagnosis of an angioinvasive mycoses. In the case of invasive aspergillosis, more than 50% of the patients have evidence of central nervous system involvement by the time the pulmonary lesion is identified [28]; therefore if focal neurologic changes or altered mental status are noted, CT scan or magnetic resonance imaging of the brain should be pursued. Radiographic findings are often nonspecific [49], ranging from diffuse infiltrates to peripheral densities or cavities [79], although the presence of an air-crescent sign on CT scan should strongly suggest infection with an angioinvasive mycoses. It should be mentioned that although our series had no zygomycete infections, these fungi could produce angioinvasive pulmonary disease in immunocompromised hosts. It is likely that they will be reported to cause infection in lung transplant patients and thus require proper culture or histopathology identification. Cultures of blood and body fluids are often unrevealing with these filamentous fungi [28].

Serum antibodies are rarely helpful in making the diagnosis of fungal infections in immunocompromised patients; measurement of serum antigens have been more informative. In disseminated Cryptococcus neoformans infection, the detection of the cryptococcal polysaccharide antigen in serum and cerebrospinal fluid is a useful diagnostic test [15]. Detection of histoplasma antigen by radioimmune assay has been reported [126] to give positive results in 50% of the serum samples and 90% of the urine samples of AIDS patients with disseminated histoplasma infection and is likely to be useful in organ transplant patients. Detection of circulating aspergillus antigen has been found [48,67,89,108] to be highly sensitive for the diagnosis of invasive aspergillosis, although in 1 study [89], false-positive results were seen in 5 of 49 patients. The level of antigenemia has also been suggested to correlate with clinical improvement [89]. The detection of candida antigen in the serum of immunocompromised patients has been studied [58,83,95]. In solid organ transplantation, candida antigen was detected in 8 of 9 liver transplant recipients with invasive candida infection and in none of the 20 patients who were not infected [121]. The clinical utility of this test in the early diagnosis of candida infection in lung transplant recipients remains to be determined. Very often the diagnosis of fungal pulmonary infection cannot be made without transbronchial biopsy and BAL. Bronchoalveolar lavage permits isolation of the pathogen in 75%-100% of the cases [71,115]. However, because of the high incidence of fungal colonization in these patients, the isolation of fungus solely by culture is difficult to interpret, especially when other organisms are present [127]. Often, further studies including transbronchial, fine-needle, or open-lung biopsies are required to make the diagnosis. Empiric antifungal therapy is often required in patients who remain febrile on broad spectrum antibiotics. Since aspergillus and candida are the most common fungal pathogens in these patients, amphotericin B is initiated until appropriate biopsies and cultures are obtained. Fluconazole is reserved for patients who cannot tolerate amphotericin

B and are likely to have infection with Candida albicans.

Because of the high morbidity and mortality associated with fungal infections in lung transplant patients, and our own fungal infection rate of 30%, efforts are being directed toward prophylactic measures for these infections. In the hospital setting laminar flow or other air filtration systems have been shown to reduce the incidence of hospital-acquired fungal infections [118]. Expense prohibits extensive use of these devices, and in 1 study [125] of heart transplant patients, isolation as the sole prophylactic measure failed to protect heart transplant recipients from developing a variety of severe infections, including fungal infections.

The use of antifungal agents for the prophylaxis of fungal infections has been studied in immunosuppressed patients, particularly leukemia and bone marrow transplant patients [22,45,50,56,84,92,103,110]. Results in 1 group of patients cannot be applied to a second group because of different risk factors and underlying pathogenic mechanisms. For example, the use of low-dose amphotericin B was shown to prevent invasive fungal infections in allogeneic marrow recipients [84,103,110], whereas a study done at our center [92] in patients receiving autologous bone marrow transplantation for breast cancer failed to reveal a difference in the incidence of invasive fungal infections between the control and the treatment group. Antifungal prophylaxis has been studied in organ transplant patients [43,78,81,94,122]. For an agent to be useful for prophylaxis in lung transplant recipients, the drug should be efficacious, safe, without significant drug interactions, and cost effective.

Since aspergillus infections are associated with the highest morbidity and mortality in this patient population, the drug used should have activity against this fungus. Of the drugs commercially available, amphotericin B and itraconazole are presently the only antifungal agents with in vivo and in vitro activity against aspergillus when used alone. In uncontrolled trials [78], the prophylactic use of intravenous amphotericin B in liver transplant patients has been shown to decrease the incidence of fungal infections. However this drug is associated with significant side effects including nephrotoxicity, especially when it is used with cyclosporine [59]. The use of low-dose intravenous amphotericin B as prophylaxis after lung transplantation did not completely prevent aspergillus infections in 1 study [70].

Because of the significant side effects associated with the use of systemic amphotericin B, other formulations have been investigated. Liposomal preparations have been shown to preserve the in vivo [44] and in vitro [6,98] antifungal activity of amphotericin B, while lacking the nephrotoxicity of intravenous delivery. Liposomal amphotericin B has been used successfully in the treatment of fungal infections in immunocompromised patients [72,105,106] including organ transplant recipients [57]. In 1 study [122], liposomal amphotericin B used for 5 days after liver transplantation was found to eliminate the risk of invasive fungal infection in the first month after transplant without significant side effects. Ringden et al [104] reported on the safety of liposomal amphotericin B (Ambisome) in 187 transplant patients receiving cyclosporine. Patients included 89 bone marrow, 64 liver, 20 renal transplant recipients, and 14 recipients of combined organs.

Other methods of amphotericin B delivery have been investigated in the prophylaxis of fungal infections. Inhaled amphotericin B has been shown to be effective in preventing and treating

fungal infections in mice [2,114] and in preventing invasive fungal infections in leukemic patients [22,56,80] and bone marrow transplant patients [50]. Preliminary reports suggest that this method of drug delivery is also efficacious in lung transplant patients. Levine et al [70] reported on their experience with antifungal prophylaxis in lung transplantation. Their prophylactic regimens included either fluconazole at 100 mg per day for 10 days, 0.2 mg/kg per day of amphotericin B for 10 days, nebulized amphotericin B at 15 mg per day for 4 weeks, or no prophylaxis. All patients received the same regimen of immunosuppressive therapy. No fungal infections were observed in the nebulized amphotericin B group, in sharp contrast to the 3 other prophylactic modalities (8 of 20 had invasive fungal infections). No adverse effects were seen with nebulized amphotericin B.

Itraconazole, a broad spectrum antifungal azole compound, has activity against candida, histoplasma, blastomyces, sporothrix, and aspergillus [27,123]. In early studies it was found to be efficacious in preventing fungal infections in lung transplant recipients [81,94] and in treating invasive aspergillosis after transplantation [27,76]. A major problem with the use of this agent in immunocompromised, postsurgical patients is its erratic absorption, which makes it uncertain whether adequate blood levels are maintained. It should also be noted that itraconazole interacts with the metabolism of cyclosporine, resulting in higher cyclosporine levels [65]. Therefore, cyclosporine levels should be monitored closely during combined therapy, and doses of the immunosuppressive drug may need to be adjusted to prevent toxicity. Although the optimal regimen for antifungal prophylaxis in lung transplant recipients is uncertain, its use should be studied in programs where the prevalence of invasive mycoses is between 10% and 15% or higher.

Summary

We reviewed the pattern and incidence of fungal infections in patients undergoing lung and heart-lung transplantation at Duke University Medical Center from September 1992 until August 1995, and present here 9 illustrative cases. Of the 73 lung and heartlung transplant recipients studied, 59 (81%) had positive fungal cultures at some point after transplantation.

The cases presented here illustrate that lung transplant recipients are predisposed to a wide variety of fungal infections. The clinical pattern of these infections ranges from asymptomatic to rapidly progressive fatal disease. In addition to the reactivation of previous fungal infections and recent exposure to new environmental sources, the donor lung itself can be the source of fungal infection, as we showed by using molecular epidemiology techniques. Because of the associated morbidity and mortality, efforts should be directed at investigating prophylactic antifungal regimens in lung transplant recipients. Preliminary reports on the use of itraconazole and aerosolized amphotericin B have been encouraging. Prospective randomized studies are needed to assess the safety and cost effectiveness of different regimens. Fungal infections in patients after lung transplantation can significantly impede recovery and lead to substantial mortality.

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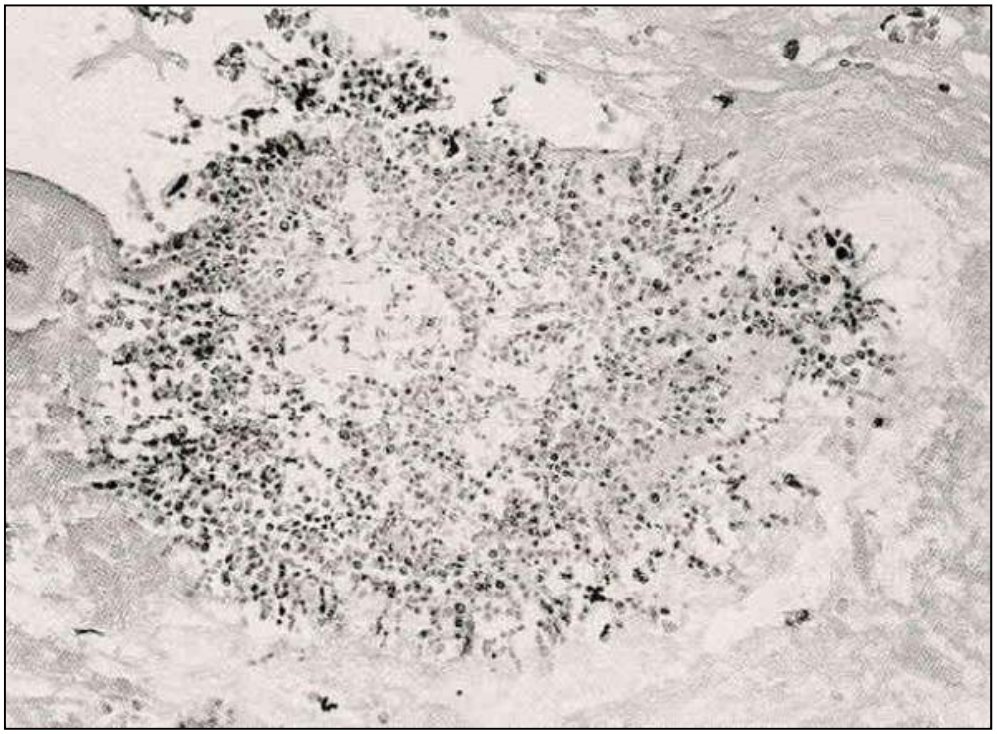

Figure 1 . Case 1. Transbronchial biopsy showing a mass of yeast and pseudohyphae adjacent to necrotic bronchial wall tissue (hematoxylin and eosin, original magnification times 170).

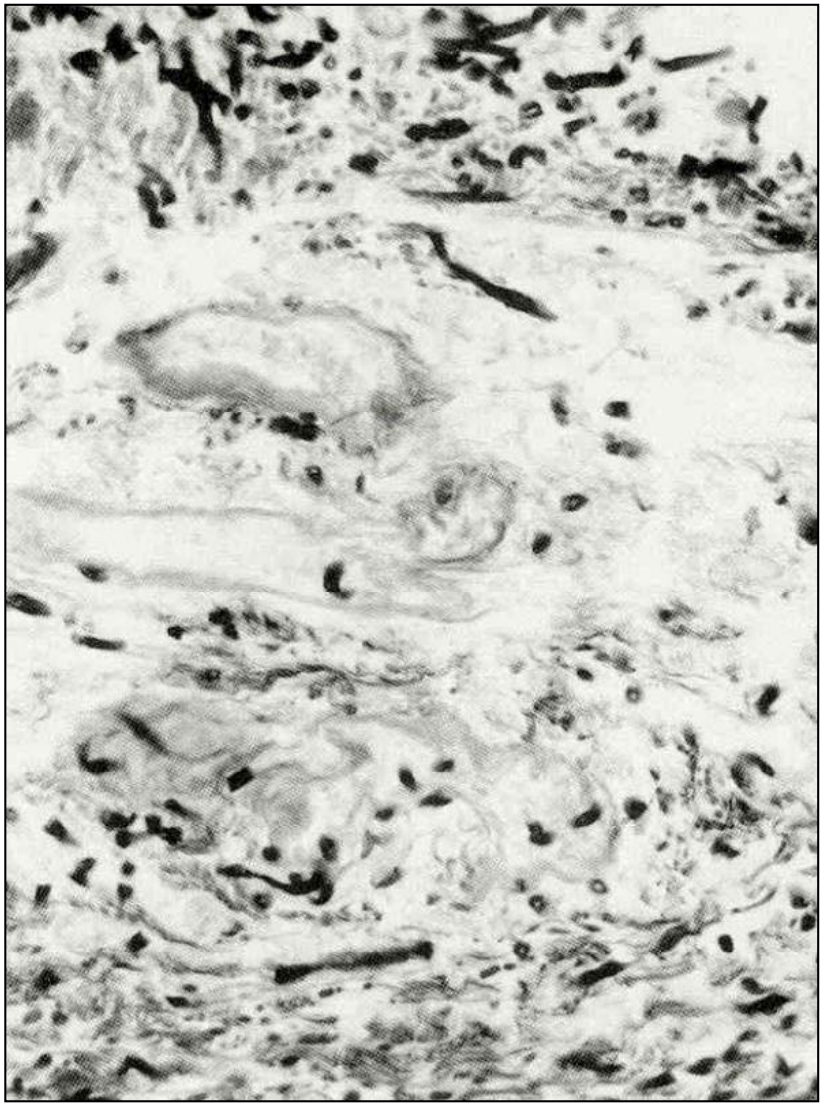

Figure 2 . Case 3. Endobronchial biopsy showing yeast and pseudohyphae infiltrating bronchial wall around vessels with associated necrosis (methenamine silver, orig. magnif. times 680).

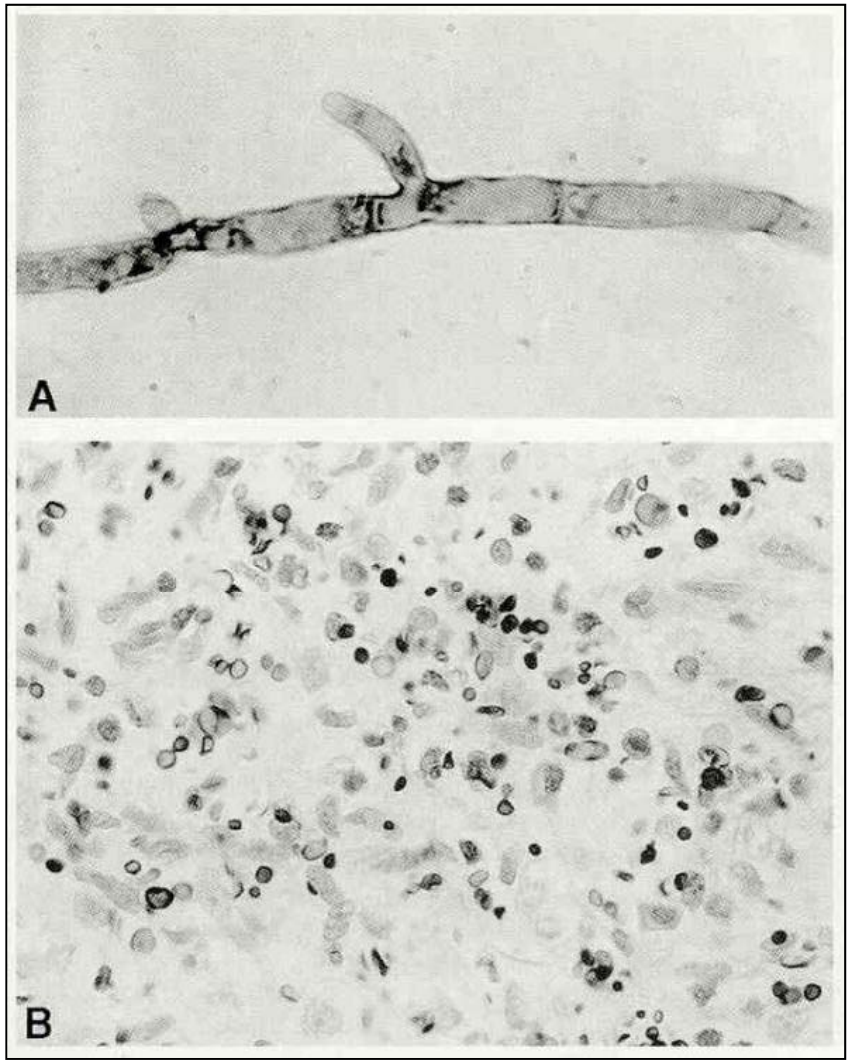

Figure 3 . Case 4. A. Septate branching hypha from bronchial lavage specimen (methenamine silver, orig. magnif. times 1,700). B. Transbronchial biopsy showing budding yeast within viable bronchial wall tissue (methenamine silver, orig. magnif. times 680).

Figure 4 . Case 5. Section of pleura taken at autopsy showing septate branching hyphae penetrating pleural surface (methenamine silver, orig. magnif. times 170).

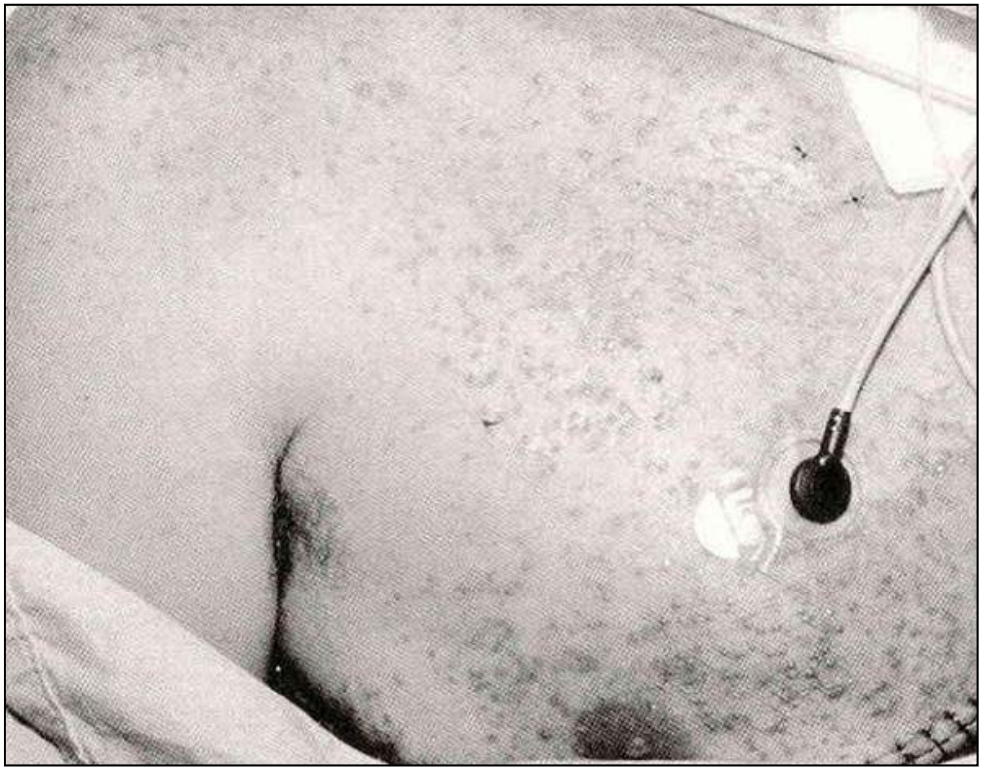

Figure 5 . Case 9. Pustular lesions seen on the chest and neck.

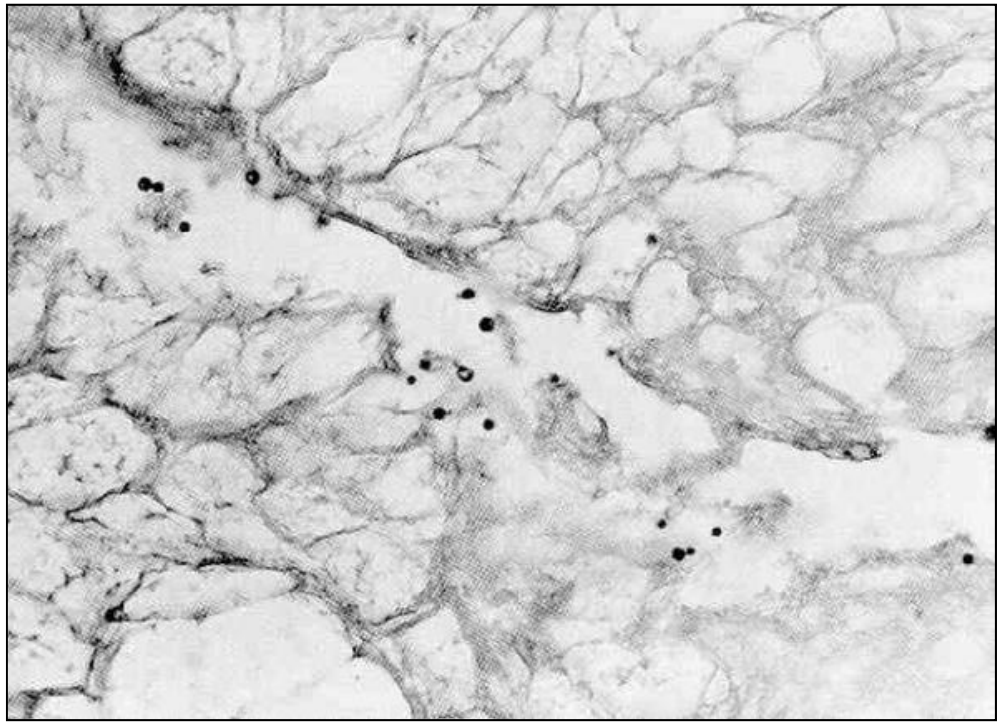

Figure 6 . Case 9. Skin biopsy showing budding yeast within the lumen of a pilosebaceous gland, morphologically consistent with malassezia (methenamine silver, orig. magnif. times 680).

Organism	No. of Patients* (n = 18)	Site (No. of Positive Cultures)			
		BAL	Sputum	Lung Biopsy	Autopsy
A. flavus	1	1	—	—	—
A. fumigatus	11	12	2	3	1
A. glaucus	1	1	—	—	—
A. niger	6	6	2	—	—
A. versicolor	5	5	—	—	—

Abbreviations: BAL = bronchoalveolar lavage.
* Some patients had more than 1 *Aspergillus* species isolated on different specimens.

Table 1 . Aspergillus species in 73 lung and heart-lung transplant recipients

Organism	No. of Patients* (n = 19)	Site (No. of Positive Cultures)			
		BAL	Lung Biopsy (Pts)	Blood (Pts)	Urine
C. albicans	15	10	6 (5)	14 (3)	13
C. tropicalis	1	1	1 (1)	—	—
C. parapsilosis	3	2	—	1 (1)	1
C. krusei	1	1	—	—	—
T. glabrata	4	1	—	—	3

Abbreviations: See previous table. Pts = patients; T. glabrata = Torulopsus glabrata.
* Some patients had more than 1 *Candida* species isolated on different specimens.

Table 2 . Candida species in 73 lung and heart-lung transplant recipients

Organism	No. of Patients (n = 4)	Site (No. of Positive Cultures)		
		BAL	Lung Biopsy	ETS
Cryptococcus neoformans	3	1	1	1
Histoplasma capsulatum	1	2	—	—

Abbreviations: See previous tables. ETS = endotracheal suction.

Table 3 . Cryptococcus neoformans and Histoplasma capsulatum

Organism (No. of Patients)*
Absidia (1)
Arthrium sp (1)
Basipetospora (1)
Bipolaris sp (1)
Chrysosporium (1)
Cladosporium (8)
Exophiala jeanselmei (3)
Fonsecaea pedrosoi (1)
Fusarium (3)
Geotrichum (4)
Paecilomyces sp (2)
Penicillium sp (16)
Rhinocladiella (1)
Scopulariopsis (1)
Trichoderma (1)
Ustilago (1)

* Some patients had more than 1 species isolated on different specimens.

Table 4 . Filamentous organisms other than aspergillus isolated from bronchoalveolar lavage