Ulcerative Tracheobronchitis after Lung Transplantation

A New Form of Invasive Aspergillosis[1-3]

MORDECHAI R. KRAMER, DAVID W. DENNING, SARA E. MARSHALL, DAVID J. ROSS, GERALD BERRY, NORMAN J. LEWISTON, DAVID A. STEVENS, and JAMES THEODORE

SUMMARY Invasive aspergillosis is frequently a fatal disease in the setting of immunosuppression, including organ transplant recipients. The fungus usually affects lung parenchyma and may disseminate from there. We have recently noted tracheobronchitis in six patients with heart-lung and lung transplants, three of whom had deep mucosal ulceration and histologic evidence of invasive aspergillosis. This apparently new form of invasive disease is initially limited to the anastomosis site and large airways. Ulceration, necrosis, cartilage invasion, and formation of a pseudomembrane are the pathologic features. In two patients subsequent disseminated aspergillosis occurred with a fatal outcome. In the two single-lung recipients, disease was limited to the transplanted side emphasizing the importance of abnormal local defense mechanisms in the airways of lung transplant recipients. Routine bronchoscopic examination of the airways is important in early detection of this complication. Oral therapy with the new, antifungal agent itraconazole was successful in five of the six patients, with fatal relapse in one. A classification of the various forms of saprophytic, allergic, and invasive forms of aspergillus tracheobronchitis, to include this new entity, is proposed.

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Introduction

Fungal infections are common causes of mortality and morbidity in organ transplant recipients (1, 2). Aspergillus infections have been reported in recipients of kidney (3, 4), heart (5, 6), and bone marrow transplants (7) as well as in heart-lung recipients (8-10). Lung transplant recipients (heart-lung, single or double lung) are particularly susceptible to respiratory tract infections as the lung is the only transplanted organ that has continuous contact with the extracorporeal environment. Fungal infections are common in this population, particularly during the first month post-transplantation. Aspergillosis accounts for more than half of these episodes. Death from invasive aspergillosis was observed in three (4%) of 75 heart-lung recipients at Stanford University Hospital.

We report here a new form of locally invasive aspergillus infection of the upper airways that has a propensity for dissemination if not treated early. The spectrum of airway involvement with aspergillus and the various therapeutic options are reviewed.

Methods

Four patients with heart-lung transplants and two single-lung transplant recipients developed severe upper airway infection with *Aspergillus* spp. between July 1989 and March 1990. Diagnosis was made in five at Stanford University Medical Center and in one at Cedars-Sinai Medical Center. The pertinent clinical features are shown in table 1. Time from transplantation to the diagnosis of aspergillosis ranged from 14 to 84 days (median, 30 days).

The follow-up in all patients included bronchoscopic examination and transbronchial biopsies at 1-wk intervals during the first month, monthly for the first 3 months, and 6 and 12 months postsurgery as part of the routine protocol after transplantation. Bronchoscopic examination included bronchoalveolar lavage (BAL) from both lingula and right middle lobe (two samples of 30 ml from each side) and four to six transbronchial biopsies from one lung with an alligator forceps. BAL specimens were cultured for bacteria (including *Legionella*), mycobacteria, fungi, and viruses (including shell vial culture for cytomegalovirus [CMV]), and cytologic examinations performed (including Papanicolaou's and Gomori methenamine silver [GMS] stains). Transbronchial and endobronchial biopsies were stained with hematoxylin-eosin, GMS, and elastin Van Gieson stains. Bronchoscopic appearance of the trachea and bronchial tree was videotaped and comparison was made between examinations. *Aspergillus* was isolated from tracheal aspirates while patients were intubated in the intensive care unit, bronchial lavage at the bronchoscopic examination, endobronchial biopsies from tracheae or bronchi, and, in one patient (Patient 3), from autopsy as well.

For quantitative recovery of *Aspergillus*, the BAL fluid was centrifuged, and all but 3 ml were removed. The remaining 3 ml were vortex-mixed, and two drops of this material were placed on each of two agar slants. The colony count was the sum of the colonies on the slants.

Therapy with itraconazole (Janssen Pharmaceutica, Beerse, Belgium) was available as part of a compassionate use trial by Janssen Pharmaceutica (four patients), and a National Institute of Allergy and Infectious Diseases Mycoses Study Group open trial of itraconazole in invasive aspergillosis (two patients). Each protocol was approved by the relevant institutional human subject review board.

All patients were immunosuppressed with monoclonal antibody OKT3 (Ortho, New Brunswick, NJ) for 14 days and triple immunosuppressive therapy: cyclosporine (4 mg/kg/day), prednisone (0.2 mg/kg/day), and azathioprine (2 mg/kg/day). All patients were receiving prophylaxis for *Pneumocystis* with trimethoprim-sulfamethoxazole. Rejection epi-

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[1] From the Department of Medicine, Divisions of Respiratory Medicine and Infectious Disease, Department of Pathology, and Department of Pediatrics, Division of Allergy, Immunology, and Respiratory Disease, Stanford University Medical Center, Stanford; the Department of Medicine, Division of Infectious Diseases and Department of Pathology, Clinical Microbiology Laboratory, Santa Clara Valley Medical Center, San Jose; the Department of Medicine, UCLA Cedars-Sinai Medical Center, Los Angeles; the California Institute for Medical Research, San Jose, California; and the National Institute of Allergy and Infectious Diseases Mycoses Study Group, Bethesda, Maryland.

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[3] Correspondence and requests for reprints should be addressed to David A. Stevens, Division of Infectious Diseases, Department of Medicine, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128.

TABLE 1

BRONCHOSCOPIC FINDINGS AND OUTCOME IN SIX ORGAN TRANSPLANT RECIPIENTS TREATED WITH ITRACONAZOLE

Age (yr)	Sex	Primary Diagnosis	Organ Transplant	Bronchoscopy: Post Tx Day	Bronchoscopy: Finding	Outcome
44	M	Cystic fibrosis	Heart-lung	14	Tracheobronchitis; multiple ulcers; suture line disruption; necrotic tissue (cartilage)	Resolution
43	M	Alpha-1 deficiency	Heart-lung	22	Tracheobronchitis; ulcers; suture line disruption; necrotic tissue (cartilage)	Resolution
34	M	PPH	Heart-lung	14	Diffuse tracheobronchitis; pseudomembrane formation	Dissemination; ampho/ death
23	F	Eisenmenger syndrome	Heart-lung	14	Tracheobronchitis; mucus plugging	Resolution, sudden death
30	M	PPH	Single lung	84	Tracheobronchitis; plugging on Tx side only	Resolution, relapse 1 month
55	M	Pulmonary fibrosis	Single lung	83	Tracheobronchitis; ulcers; necrotic tissue (cartilage) Tx side only	Resolution, relapse 1 month; lung invasion; ampho/death

Definition of abbreviations: PPH = primary pulmonary hypertension; Tx = transplantation; Ampho = amphotericin B.

sodes were treated with three daily doses of methylprednisolone followed by an increase in orally administered prednisone, which was then decreased to the baseline dose within 2 wk.

Itraconazole serum concentrations were measured in all patients by bioassay as previously described (11).

Results

Clinical Presentation

In general, patients were asymptomatic. Mild cough was present in two patients. Fever and leukocytosis were observed in one patient only, but they were thought to be related to a concomitant severe rejection episode. Chest radiographs were clear in four patients. Bilateral interstitial infiltrates were observed in two patients; one had concomitant CMV pneumonitis, and the other had severe lung rejection.

Bronchoscopic Findings

In the follow-up period, 42 bronchoscopic examinations with transbronchial biopsies were performed (mean of seven per patient) (table 1). In three patients multiple ulcers were observed in the anastomosis area and distal to it. The suture line was disrupted in two of these patients, and sutures became loose in the lumen. The ulcers were covered with necrotic material. In the other three patients, severe tracheobronchitis was observed with red edematous mucosa. In one patient a pseudomembrane covered the trachea and bronchi distal to the anastomosis. Mucus plugging was seen in the bronchial segments. Although bilateral lesions were observed in the heart-lung transplant recipients, in the two patients with single lung transplants, the inflammatory changes were confined to the transplanted side only, around and distal to the anastomosis, without any lesions on the native lung.

Pathologic Examination

Transbronchial biopsies. Transbronchial biopsies did not show evidence for parenchymal invasive aspergillosis at any time. In five patients, evidence of rejection was observed in some biopsies (table 2). In four instances, the patients' rejection episodes preceded the aspergillus infection, and in one the diagnosis of rejection was made after antifungal therapy had been instituted. In two patients, concomitant CMV pneumonitis was observed.

Endobronchial biopsies. In three patients, endobronchial biopsies of necrotic material covering the anastomosis or bronchial ulceration were performed. In all three, necrotic cartilage was seen invaded by large amounts of septate narrow-angle branching hyphae.

Cytologic examination. GMS stain of BAL fluid was positive for hyphal elements in all patients.

Microbiologic Studies

Bacterial cultures. In addition to the *Aspergillus* spp. cultured, most patients also had positive bacterial cultures.

Viral cultures. CMV was cultured in the two patients who showed concomitant CMV pneumonitis histologically in their transbronchial biopsies.

Fungal cultures. The quantitative results are shown in figure 1. Higher counts generally reflected disease severity as determined visually at bronchoscopy.

Treatment and Outcome

All patients were treated with itraconazole orally 200 mg twice a day after a loading dose of 200 mg three times a day for 4 days. Two patients (Patients 2 and 4) received some amphotericin B prior to itraconazole therapy (total dose of 336 and 30 mg, respectively). Two patients were given amphotericin after discontinuation of itraconazole (see below).

Steady-state itraconazole serum concentrations ranged between 0.3 and 21 μg/ml. In Patient 1, concentrations were low (< 2 μg/ml), and the dose was increased to 300 mg twice a day, whereas in Patient 6, concentrations were high (> 20 μg/ml), and the dose was adjusted to 100 mg twice a day.

Resolution was seen endoscopically after 4 to 12 wk in all patients (except Patient 3), with resolution of the inflammation and mucus plugging and disap-

TABLE 2

PROPOSED CLASSIFICATION OF TRACHEOBRONCHIAL ASPERGILLOSIS

Disease Entity	Clinical Features	Pathologic Features	Serologic Features	References
Invasive				
Aspergillus bronchitis or tracheobronchitis	Dyspnea, wheezing, cough, and hemoptysis; slight inflammation of bronchi or trachea with mucus exudate containing heavy growth of *Aspergillus* spp.	Acute or chronic inflammatory cell infiltrates, hyperemia and squamous metaplasia; superfical hyphae noted	No data	This article, 19, 20, 21
Ulcerative aspergillus bronchitis	All the above together with focal ulceration, single or multiple	As above with areas of ulcerative necrosis; often debris reveals hyphae invading degenerate cartilage or other tissue	No data	This article, 20
Pseudomembranous aspergillus tracheobronchitis	Severe dyspnea because of airway obstruction by membrane. Extensive grey/white/black membrane extending over most of trachea or fungal casts that overlie friable hemorrhagic necrotic mucosa	Membrane a mass of mycelia with necrotic material containing mucus and red and white cells; extensive necrosis in underlying tissue	No data	This article, 17, 19, 20, 23, 24
Saprophytic				
Mucoid impaction of the bronchi	Asthma, cough, upper respiratory infection, fever, chest pain, production of casts, hemoptysis, dyspnea; upper lobe involvement; chronic onset	Secondary or tertiary bronchial involvement with bronchial wall thinning, inflammation with eosinophils (50%), distal bronchiectasis, and chronic pneumonitis	None	25
Obstructing bronchial aspergillosis	Cough, dyspnea, hemoptysis, chest pain, fever, production of fungal casts; lower lobe involvement; subacute onset in AIDS	Multiple fungal casts probably in all bronchial divisions; no histologic data	No data	23
Allergic				
Allergic bronchopulmonary aspergillosis	Asthma, cough, production of fungal casts, eosinophilia, central bronchiectasis, and variable radiologic findings	Bronchi contain mucus, fibrin, Curschmann's spirals, Charcot-Leyden crystals, eosinophils, and mononuclear cells	Elevated IgE, *Aspergillus*-specific IgE and IgG	26
Bronchocentric granulomatosis				
Group I	Asthma and eosinophilia frequent, fever, cough, wheezing, dyspnea, and chest pain in young adult; elevated ESR*	Granulomas with necrotic zones containing large numbers of eosinophils and some with Charcot-Leyden crystals and fungal hyphae, some with mucus plugs in small bronchi and/or distal eosinophilic pneumonia	Negative	22, 27
Group II	Fever, cough, wheezing, dyspnea, and chest pain in older patients; elevated ESR	Granulomas with necrotic zones containing neutrophils and few eosinophils	Negative	22, 27

* ESR = erythrocyte sedimentation rate.

pearance of the ulcers. Cultures for *Aspergillus* spp. from bronchoscopic examination were negative in these patients after 4 to 12 wk of initiating therapy with itraconazole. The sutures remained loose in the lumen in one patient, but the anastomosis did not dehisce. Patient 3 developed respiratory failure and required mechanical ventilation, which prevented administration of itraconazole. Amphotericin was therefore given at a dose of 0.5 mg/kg/day. This failed to arrest his infection, and he died 4 wk later with disseminated aspergillosis in lungs, brain, heart, and liver. Patient 6 had deterioration of chronic hepatitis after 12 wk of therapy, and therefore itraconazole was discontinued. BAL cultures were negative for *Aspergillus* spp. at that time. Six weeks later, after an episode of rejection, *Aspergillus* was again cultured from BAL, and amphotericin was instituted. The patient died 4 wk later from hemorrhagic pulmonary aspergillosis, polymicrobial sepsis, and renal failure. Patient 4 died suddenly at home. Autopsy as well as fungal cultures showed no evidence of fungal disease. The cause of death remains unknown.

Discussion

Invasive aspergillosis is one of the most devastating opportunistic infections encountered in the transplant setting (1–7). Symptoms are often minimal or absent initially, leading to delay in diagnosis and therapy. The diagnosis usually requires one or more invasive procedures (12, 13). Pulmonary infection is the most frequent disease and commonly involves lung parenchyma. Renal, heart, as well as bone marrow transplant recipients are commonly affected, with high fatality rates (4–7). At Stanford University Hospital, aspergillus infection was encountered in 15% of all heart-lung transplant recipients (unpublished data).

Pulmonary infections are more common in lung transplant recipients than in other organ recipients. Transferring lungs from donor to recipient with current techniques results in denervation of the lungs and airways, thus abolishing important reflexes. Cough reflex is ab-

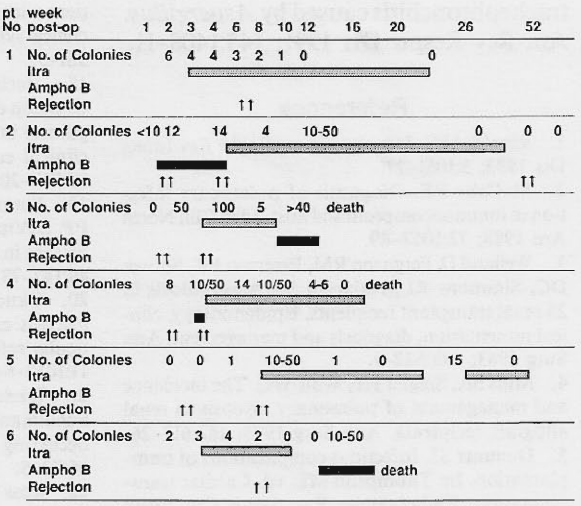

Fig. 1. Clinical course and fungal culture results from BAL in correlation with the antifungal therapy (*shaded bars*) and rejection episodes (*arrows*) in six patients with invasive tracheobronchitis (itra = itraconazole; ampho = amphotericin B).

sent distal to the tracheal or bronchial anastomosis (14). Mucociliary clearance is also impaired (15). The anastomosis site is particularly vulnerable to local pathogen colonization, as suture material is present that initiates a local immune response (16). Ischemic cartilage is particularly susceptible to bacterial and fungal infections. Rejection episodes leading to airway inflammation results in a good milieu for colonization and infection, particularly as rejection treatment also increases the intensity of immunosuppression. Other specific problems that affect lung transplant recipients are acquisition of infection from the donors' lungs or autocontamination from the native lung in single lung recipients. In our patients, all donor cultures were negative for *Aspergillus* spp. immediately prior to transplantation.

The new entity we describe here of invasive ulcerative tracheobronchial aspergillosis is probably an early form of invasive disease that, undetected, can easily disseminate and be fatal. This form of infection appears to be highly specific to lung and heart-lung transplantation apart from other rare instances in other host groups (17, 18).

Fiberoptic bronchoscopy has allowed both study and localization of these infections that were previously studied at autopsy. Three morphologic forms of disease were seen in our patients: tracheobronchitis, ulcerative bronchitis, and psuedomembranous bronchitis. It is possible that all three forms represent a progressive spectrum of disease ranging from mild bronchitis through an ulcerative form to a widespread pseudomembranous diffuse disease. All three forms of disease were invasive as is confirmed by the histologic examination of endobronchial biopsies from these areas. The biopsies showed hyphae invading cartilage under the necrotic material covering these ulcers or inflamed mucosa.

Tracheal and bronchial invasive aspergillosis have been previously reported under various descriptive terms: aspergillus bronchitis (10), pseudomembranous necrotizing bronchial aspergillosis (17), necrotizing tracheobronchial aspergillosis (18), aspergillary bronchitis (19), tracheopulmonary mycosis (20), and bronchocentric mycosis (21). The vast majority of these lesions are recognized only at autopsy, and the terms used to describe each reflect a pathologic bias. Based on the comparison of our cases with those previously described, we suggest that the term invasive bronchial aspergillosis be used to convey all of these entities (table 2). When the pathologic or bronchoscopic appearance is known, one of the three terms should be used: aspergillus bronchitis/tracheitis or, with the appropriate features, ulcerative aspergillus bronchitis/tracheitis or pseudomembranous aspergillus bronchitis/tracheitis.

Invasive aspergillus bronchitis occurring in heart-lung transplant recipients has been mentioned briefly in the literature previously. The cause of death in one patient was attributed to "aspergillus bronchitis," but no further data were provided (10). More recently (21), a pathologic entity "bronchocentric mycosis" was described in three transplant patients (two were heart-lung recipients). In one of the patients, bronchoscopic examination showed bronchitis with mucus plugging, and the other two had invasive fungal pneumonia with features resembling bronchocentric granulomatosis.

The frequency of invasive tracheobronchitis in lung transplant recipients suggests that the unusual local host factors peculiar to lung transplantation promote this pattern of infection. This hypothesis is strongly supported by the two single lung recipients in whom the pathologic process seemed to be limited to the transplanted lung. In both cases the anastomosis site was involved as well as the large airways distally.

Invasive aspergillosis of the tracheobronchial tree has also been reported in a nontransplant immunocompromised population. A case of necrotizing pseudomembranous bronchitis was reported in a patient with acquired immunodeficiency syndrome (AIDS) (17). Two leukemic patients who developed airway obstruction caused by necrotizing tracheobronchitis with aspergilloma (mycetoma) formation in the bronchial lumen have been reported (18). It thus appears that in the setting of intense immunosuppression (AIDS, leukemia/granulocytopenia), aspergillus infection can, although rarely, involve the tracheobronchial tree.

In less immunocompromised and nonimmunocompromised settings the finding of *Aspergillus* spp. in the airways is considered on many occasions to represent saprophytic colonization. Defining the line between pathogen and commensal is sometimes difficult. Noninvasive diseases include allergic bronchopulmonary aspergillosis (ABPA) (22) and the newly described entity, obstructing bronchial aspergillosis in patients with AIDS (23). We feel it is useful to classify and provide a more detailed description of the various forms of airway involvement with *Aspergillus* to allow direct comparison with invasive aspergillus bronchitis and for uniformity in future publications (table 2).

The treatment of invasive aspergillosis remains problematic (28). Although intravenously administered amphotericin B treatment is frequently successful in renal and cardiac transplant recipients if the diagnosis is made early (4, 7), there is the problem of synergistic nephrotoxicity with cyclosporine (29). We tried to avoid this problem by using orally administered itraconazole. This agent has shown promising results, comparable with amphotericin B, in uncontrolled trials for invasive pulmonary aspergillosis in nonneutropenic patients (30–33). In this study, in four patients who could take itraconazole by mouth, therapy was successful. In one patient in whom therapy failed, its administration was stopped during the period when he was intubated. In the sixth patient, therapy was stopped because of possibly associated hepatitis, with subsequent recurrence and pulmonary invasive aspergillosis. Data

from published (32) and unpublished observations suggest that serum itraconazole concentrations are important in determining efficacy; a serum concentration of ≥ 5 μg/ml is associated with clinical efficacy. Caution, however, should be exercised when administering cyclosporine with itraconazole as we have documented a significant interaction (increase in cyclosporine concentration) between the drugs (34).

The appropriate duration of therapy for invasive aspergillosis is not known. We have treated our patients with itraconazole for 4 to 6 months until repeated bronchoscopic examinations were negative. In two patients (Patients 5 and 6) therapy was stopped after 3 to 4 months. Recurrence of mild aspergillus bronchitis was noted in one, but endobronchial biopsies did not show invasive disease. In the other, we noted fatal lung tissue invasion after increased immunosuppression. We feel that at least 6 to 12 months of treatment is probably necessary to eradicate the fungus.

The high incidence of aspergillus infection in the first month posttransplantation suggests that the disease is nosocomially acquired. Prophylactic therapy for prevention of aspergillus infection is probably justified in centers with high aspergillus infection rates, particularly in the early posttransplantation period. Further studies are necessary in order to evaluate this.

In conclusion, we have described a new form of invasive aspergillosis that involves the large airways. This entity appears to be common in lung transplant recipients and is probably related to abnormalities in the local defense mechanisms of the airways. Early detection by routine bronchoscopic examination is crucial for successful therapy. The new, antifungal oral agent itraconazole has the potential of curing this disease without significant toxicity.

Note added in proof: Two relevant articles recently appeared that describe syndromes related to those in our study. A. Clark, J. Skelton, R.S. Fraser, *et al.* Fungal tracheobronchitis. Report of 9 cases and review of the literature. Medicine 1991; 70:1–14. D.W. Hines, M. Haber, L. Yaremko, *et al.* Pseudomembranous tracheobronchitis caused by *Aspergillus*. Am Rev Respir Dis 1991; 143:1408–11.

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