Aspergillus and Endobronchial Abnormalities in Lung Transplant Recipients*

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Study objective: To determine the relationship between aspergillus recovery from the airways of lung transplant recipients and the development of endobronchial abnormalities.

Design: Retrospective case series.

Setting: Tertiary-care hospital.


Measurements and results: The study cohort included 38 patients. The primary end point was the bronchoscopic identification of an endobronchial abnormality. Aspergillus was isolated from the lungs of nine patients (23.7%). Most of these isolates occurred early after transplantation (mean, 8 weeks). Endobronchial abnormalities arose in seven of the patients (18.4%) and manifested as either exuberant granulation tissue or stricture formation. Six of the 9 (66.6%) patients with aspergillus developed airway lesions, compared to 1 of the 29 patients (3.4%) without aspergillus (p = 0.0002). Endobronchial abnormalities were 19.3 times more likely to occur in patients in whom aspergillus had previously been isolated. As a screening test for the subsequent diagnosis of an airway complication, the recovery of aspergillus had a sensitivity and specificity of 85.7% and 90.3%, respectively. These aspergillus-related endobronchial abnormalities were clinically relevant as evidenced by a mean increase of 25.9% in the FEV1 after bronchoscopic intervention.

Conclusion: The early isolation of aspergillus from the airways of lung transplant recipients identifies patients at increased risk for the development of clinically significant endobronchial abnormalities.

B bronchial anastomotic problems are the commonest mechanical problem seen in lung transplant recipients.1–4 The anastomotic site has always been regarded as a “watershed” area, since the bronchial circulation is sacrificed during the transplant procedure. In the early days of transplantation, an omentopexy was performed routinely in an attempt to augment the blood supply to the anastomosis. In addition, the early avoidance of steroids was also believed to facilitate healing at the anastomotic site. Both of these concepts have since been refuted.4 Nonetheless, the bronchial anastomosis does remain prone to stricture/granulation tissue formation that is thought to be ischemic in origin.

Aspergillus colonization and infection of the airways is also a common complication after lung transplantation. Patients are predisposed to this through immunosuppression and the organism having direct access to the allograft. Other contributory factors may include reduced mucociliary clearance, pulmonary denervation, and nosocomial acquisition.

Although anastomotic problems and aspergillus infection are two common maladies after lung transplantation, their relationship is not well defined. We report a strong association between aspergillus in the airways and the subsequent development of endobronchial abnormalities.

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Abbreviations: AREA = aspergillus-related endobronchial abnormalities; CI = confidence interval; EGT = exuberant granulation tissue
Materials and Methods

Subjects

We reviewed the records of all patients who underwent lung or heart-lung transplantation at our institution between December 1991 and June 1999. This cohort included 38 patients (15 men and 23 women), with a mean ± SD age of 49.9 ± 9.9 years. In 31 cases, single lung transplantation was performed; in six instances, bilateral lung transplantation was done; and there was one heart-lung recipient. There were therefore a total of 44 anastomoses in the study group. These were performed end to end using a running 4-0 Prolene suture (Ethicon; Somerville, NJ) for the membranous bronchus, and either an interrupted or a running Prolene suture for the cartilaginous portion. The single lung recipients included 22 patients with COPD and 9 patients with idiopathic pulmonary fibrosis. The bilateral lung recipients' disease processes were as follows: lymphangioleiomyomatosis (n = 2), Eisenmenger's complex (n = 2), COPD (n = 1), and cystic fibrosis (n = 1). The heart-lung recipient was a patient with Eisenmenger's syndrome.

Immunosuppression consisted of triple therapy with cyclosporine, azathioprine, and prednisone for the first 12 patients (from 1991 to September 1996), and tacrolimus, azathioprine, and prednisone for the next 26 patients (from October 1996 to 1999).

Bronchoscopies were performed as clinically indicated for the first 12 patients, while a surveillance protocol was implemented thereafter. For the latter patients, bronchoscopy was performed on posttransplant days 5, 10, and 30, and every 3 months for the first year. In addition, bronchoscopies continued to be performed as clinically indicated. Clinical indications for bronchoscopy included decrements in flow rates, infiltrates on chest radiographs, unexplained fevers, or leukocytosis. Fungal studies were routinely sent with all bronchoscopies. Endobronchial biopsies and/or brush cultures were performed for any endobronchial abnormality. Pulmonary function testing was done with a pneumotach spirometer (Sensor Medics; Yorba Linda, CA), and the equations of Crapo et al.5 were used for reference values.

End Points

The major study variable of interest was the presence of aspergillus. This was classified further as either colonization or infection. Colonization was defined as a positive culture in the absence of significant endobronchial lesions. Aspergillus infection was defined by the presence of endobronchial lesions from which there was biopsy evidence of local aspergillus infection. The primary study end point was the development of an endobronchial lesion defined as either (1) a stricture, or (2) the presence of exuberant granulation tissue (EGT) in the airway. For the patients with aspergillus, the subsequent development of endobronchial complications is henceforth referred to as aspergillus-related endobronchial abnormalities (AREA). A secondary end point was the time between the recovery of aspergillus and the development of an airway complication. We also determined if a reduction in spirometric indexes preceded the diagnosis of airway lesions and whether endobronchial interventions (laser, stent placement) improved spirometry. A reduction in FEV_1 > 10% was regarded as significant.

Statistical Analysis

Continuous variables were analyzed using a t test, while a Fisher's Exact Test was employed for categorical variables. All tests were two sided. The sensitivity, specificity, positive predictive value, and negative predictive value of the presence of aspergillus at predicting the subsequent development of an endobronchial complication were computed via a standard 2 by 2 table. To account for possible bias because of the introduction of the surveillance bronchoscopy protocol, two different analyses were performed. First, all patients were analyzed as one cohort, and then a separate subgroup analysis was done of the subjects transplanted after the surveillance program and change in immunosuppression were instituted. A p value of <0.05 was assumed to represent statistical significance, and 95% confidence intervals (CIs) are reported where appropriate.

Results

Aspergillus was isolated in a total of 9 of 38 patients (23.7%). All isolates were of the Aspergillus fumigatus subtype. Endobronchial complications were diagnosed in seven patients (18.4%). Of these, two patients developed a stricture and five patients developed EGT. A typical example of the latter is shown in Figure 1. Six of the nine patients (66.7%) from the aspergillus cohort developed airway complications, as compared to 1 of 29 patients (3.4%) in whom aspergillus was not isolated (p = 0.0002). Endobronchial abnormalities were therefore 19.3 times (95% CI, 2.7 to 140.1) more likely in patients from whom aspergillus was isolated. In the subgroup of 26 patients transplanted after the initiation of the surveillance bronchoscopy protocol and the switch to tacrolimus, there were eight positive aspergillus cultures and six airway complications. As with the entire cohort, all but one of these complications occurred in patients from whom aspergillus was previously recovered (p = 0.004). In this subgroup, isolation of aspergillus conferred a 11.3-times greater risk (95% CI, 1.6 to 81.4) of a subsequent endobronchial complication.

The significance of aspergillus recovery as a screening test to predict airway lesions is shown in Table 1. For the entire cohort, the sensitivity and

Figure 1. Excess granulation tissue at the left bronchial anastomosis (patient 2).
specificity of the test were 85.7% and 90.3%, respectively. For the patients transplanted during the surveillance program/tacrolimus era, the sensitivity and specificity were 83.3% and 85%, respectively. For both the entire cohort and the subgroup, the negative predictive value was > 94%.

All patients in whom aspergillus was isolated were treated. Treatment consisted either of oral itraconazole, 200 to 400 mg/d for 3 months, or IV amphotericin B for 1 month followed by oral itraconazole for an additional 2 to 3 months. In some cases, inhaled amphotericin B was added at doses ranging from 15 to 25 mg bid for 1 to 3 months.

The characteristics of the six patients with AREA are shown in Table 2. In four of the six cases, the AREA first took the form of pseudomembrane formation, with these patients shown to have aspergillus bronchitis via endobronchial biopsy. In all these cases, the aspergillus was noted to be locally invasive with evidence of invasion into adjacent cartilage. In one of these patients, the AREA subsequently took the form of a distinct stricture at the right middle lobe orifice. The remaining patients had EGT narrowing the airway lumen; in most cases (four of six cases), the anastomosis was the site of the abnormality. In the remaining patient, the EGT was in the native bronchus of the transplant side proximal to the anastomosis. Four of the six patients required placement of an endobronchial stent: one Wallstent (Schneider; Geneva, Switzerland) and three Ultraflex stents (Microinvasive; Boston, MA). One patient was treated with laser ablation, and one lesion was debrided via rigid bronchoscopy and subsequent balloon dilatation.

The median time between transplantation and the first isolation of aspergillus was 8 weeks (range, 3 to 35 weeks). In all cases, the aspergillus was isolated via bronchoscopy. Four of the cases of aspergillus infection/colonization occurred in a 1-month time period coincident with new construction being initiated at the hospital. The median time that AREA was diagnosed after the initial aspergillus isolation was 6 weeks (range, 1 to 23 weeks). The median time after the initial isolation of aspergillus to the first decrement in flows that could be attributed to their anastomotic problem in these patients was 11 weeks (range, 1 to 57 weeks). In two of the patients, there was a significant decrement in their FEV1 before the anastomotic problem was identified; in three patients, the anastomotic problem was identified prior to a significant decrement; and in one patient, both occurred simultaneously. The impact of the various interventions for the AREA is shown in Figure 2. The best FEV1 was the patient’s prior baseline as defined by the International Society for Heart and Lung Transplantation guidelines. Among the six patients, the mean improvement in the FVC and the FEV1 were 11.3% (p = 0.084) and 25.9% (p = 0.022), respectively. Flow reduction in patient 6 occurred 57 weeks after the identification of EGT, and was likely secondary to bronchiolitis obliterans. The anastomosis was ultimately stented with only marginal improvement in her flow rates. Excluding this patient and patient 4 (right middle lobe stricture), the mean improvement in the FEV1 would have been even greater (600 mL or 49.5%). The mean time interval between the preintervention and postintervention spirometry was 12 days (range, 0 to 32 days).

<table>
<thead>
<tr>
<th>Patient No./Primary Diagnosis</th>
<th>Tx Type</th>
<th>Infection vs Colonization</th>
<th>Pseudomembrane</th>
<th>AREA</th>
<th>Location</th>
<th>Rx</th>
<th>( \Delta \text{FEV}_1 ), mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/IPF</td>
<td>RSLT</td>
<td>Infection</td>
<td>Yes</td>
<td>EGT</td>
<td>RMS</td>
<td>Laser</td>
<td>290 (21)</td>
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<tr>
<td>2/IPF</td>
<td>LSLT</td>
<td>Infection</td>
<td>Yes</td>
<td>EGT</td>
<td>LMS</td>
<td>Stent</td>
<td>1000 (68)</td>
</tr>
<tr>
<td>3/COPD</td>
<td>LSLT</td>
<td>Colonization</td>
<td>No</td>
<td>EGT</td>
<td>LMS</td>
<td>Stent</td>
<td>720 (71)</td>
</tr>
<tr>
<td>4/COPD</td>
<td>LSLT</td>
<td>Infection</td>
<td>No</td>
<td>EGT</td>
<td>LNB</td>
<td>Stent</td>
<td>370 (38)</td>
</tr>
<tr>
<td>5/COPD</td>
<td>RSLT</td>
<td>Infection</td>
<td>Yes</td>
<td>Strict</td>
<td>RML</td>
<td>Balloon</td>
<td>150 (8.6)</td>
</tr>
<tr>
<td>6/IPH</td>
<td>BLT</td>
<td>Colonization</td>
<td>No</td>
<td>EGT</td>
<td>LMS</td>
<td>Stent</td>
<td>100 (9.5)</td>
</tr>
</tbody>
</table>

*IPF = idiopathic pulmonary fibrosis; PH = pulmonary hypertension; RSLT = right single lung transplant; LSLT = left single lung transplant; BLT = bilateral lung transplant; Strict = stricture; RMS = right mainstem bronchus; LMS = left mainstem bronchus; LNB = left native bronchus; RML = right middle lobe; Rx = therapeutic intervention; \( \Delta \text{FEV}_1 \) = change in the FEV1 preintervention and postintervention; Tx = treatment.

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**Table 1—Role of the Presence of Aspergillus in Predicting Airway Abnormalities**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Entire Cohort</th>
<th>Surveillance Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 38 )</td>
<td>( n = 26 )</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>85.7</td>
<td>83.3</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>90.3</td>
<td>85</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>66.6</td>
<td>62.5</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>97.6</td>
<td>94.4</td>
</tr>
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</table>
We report a strong association between aspergillus infection and the subsequent development of clinically significant endobronchial abnormalities (AREA) in a cohort of lung transplant recipients. This AREA mostly took the form of excess granulation tissue at the anastomosis; however, one patient developed a stricture at his right middle lobe orifice and another developed granulation tissue proximal to the anastomosis. The location of the granulation in this latter patient tends to discount the role of bronchial ischemia and lend further credence to the role of aspergillus. It is important to note that in all cases, the bronchoscopic isolation of aspergillus preceded the diagnosis of airway lesions; this serves to dispel the notion that abnormal endobronchial tissue might have been the initiating event, and that this might have then provided a nidus for the aspergillus. In the cases in whom inhaled amphotericin B was utilized, this was only employed after the development of endobronchial abnormalities, and therefore was unlikely to have been a causative factor.

There have been reports of excess granulation tissue at the anastomosis in lung transplant recipients, but to our knowledge, this is the first report of its association with aspergillus. There is an association between stricture formation and the subsequent predisposition to infection; however, this was not the case in our series, since there was no evidence of stricture formation or abundant granulation tissue with the first aspergillus isolate in any of the cases. Granulation tissue reactions in response to infection within the lung parenchyma have been reported, and it is possible that aspergillus infections within the airways can cause a similar exuberant response. The granulation tissue occurred subsequent to pseudomembrane formation in four of the six patients, and therefore was likely the result of the healing process of these pseudomembranes. It is important to note that the median time for initial aspergillus isolation in our population was approximately 8 weeks. Therefore, our findings might only be applicable to early aspergillus isolation after transplantation. It is noteworthy too that the lesions are amenable to standard bronchoscopic interventions that mostly involved stent placement in our cohort of patients.

The predictive power of a positive aspergillus isolate for a subsequent anastomotic problem may have important clinical ramifications, since a drop in flows in a patient with a prior positive culture may herald the development of pathology at the anastomosis. More frequent pulmonary function testing in such patients may be indicated, and follow-up surveillance bronchoscopies in all patients who have a prior positive aspergillus culture should be considered.
Our study has several limitations: firstly, the retrospective design of the study exposes the results to bias. However, since we focused on end points with objective definitions and since complete data for all patients was available, the impact of any bias should be small. Secondly, the change in our protocol with the implementation of surveillance bronchoscopies and the switch to tacrolimus did not appear to influence our findings. Lastly, our sample size was relatively small; to account for this, we reported the 95% CIs for the odds ratios, and in each analysis, the lower bound of the CI was > 1.5.

In summary, the early isolation of aspergillus in patients who have undergone lung transplantation is associated with the development of clinically significant endobronchial abnormalities. The recovery of aspergillus may predict the development of these lesions and the resultant expiratory flow reduction.

REFERENCES