Outcome of Lung Transplantation in Patients With Mycetomas*

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Background: Lung transplantation has become an acceptable treatment option for many end-stage lung diseases. Pulmonary mycetomas are found in patients with end-stage lung diseases, especially sarcoidosis. The clinical course and long-term outcome of these patients after transplantation remains unknown.

Methods: We reviewed retrospectively the pathology reports of the explanted lungs from all lung and heart-lung transplantations performed at our institution between January 20, 1992, and June 26, 2000. Patients were included in our study if mycetomas were present on the specimens. Information on transplant date and type, diagnosis, information on antifungal therapy and fungal infections pretransplant and posttransplant, and clinical course after transplantation was recorded.

Results: Mycetomas were present in 3.0% of transplant recipients (9 of 303 patients). The underlying pulmonary diagnoses were sarcoidosis (six patients), and emphysema, idiopathic pulmonary fibrosis, and pneumoconiosis (one patient each). Seven patients received bilateral lung transplants, one patient received a heart/lung transplant, and one patient received a single lung transplant. Aspergillus was isolated from culture in five patients pretransplant and from five patients posttransplant. Six patients received treatment with itraconazole, or IV or inhaled amphotericin B prior to transplantation. All patients who survived transplantation received posttransplant antifungal therapy. Four patients died in the first month after transplantation. Two patients died at 17 months and 24 months posttransplant, respectively; one patient received a second transplant 30 months later; and two patients are alive and free from fungal infections 17 months and 18 months, respectively, after transplantation. All of the medium-term survivors received lengthy therapy with inhaled and systemic amphotericin B and itraconazole before and after transplantation.

Conclusions: Lung transplant recipients with mycetomas have significantly reduced posttransplant survival. Careful selection of patients and aggressive antifungal therapies before and after transplantation have led to improved outcomes in patients with mycetomas. Additional research is needed to define the best therapeutic strategy for these patients during transplantation.

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Key words: fungal infections; lung transplantation; mycetomas; sarcoidosis

L ung transplantation is an acceptable treatment option for end-stage lung disease. As of 1999, > 10,000 lung transplants have been performed in North America. The number of transplantations performed each year has remained slightly > 1,000/yr, but > 3,000 patients are currently on the lung transplantation waiting list. The lack of donor lungs makes appropriate allocation of organs very important. Potential donors are selected by employing

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tality rate (5 to 13%) as well as postoperative complications.\(^4\)\(^-\)\(^5\) Currently, mycetomas are considered a strong relative contraindication for lung transplantation.\(^4\) Consistent with that view, we have previously described\(^9\) a patient with mycetomas who received a heart/lung transplant for end-stage sarcoidosis and died from disseminated Aspergillus infection. (This patient is included in the following report.) In addition, patients with mycetomas frequently have extensive pleural fibrosis, making lung resection difficult at the time of transplantation. There are no other previous reports on the outcome of patients with mycetomas undergoing lung transplantation.

According to other reports,\(^10\)\(^-\)\(^12\) the survival of patients with sarcoidosis undergoing lung transplantation is worse compared to patients with other diagnoses and there is frequent recurrence of sarcoidosis in the transplanted lungs. It is not known whether the presence of mycetomas explains the decreased survival of these patients.

This study was performed in order to better assess the characteristics and the outcomes of patients with mycetomas who received lung transplants at our institution. Their outcomes were compared to those of the rest of the patients undergoing lung transplantation in our institution.

**Materials and Methods**

We performed a retrospective review of the pathology reports of the explanted lungs of all patients undergoing lung or heart/lung transplantation in our institution between January 10, 1992, and June 26, 2000. Although mycetomas were considered a relative contraindication to lung transplantation in our institution, we evaluate these patients on a case-by-case basis. Patients were included in the current analyses if mycetomas were found on examination of the explanted lungs. A typical specimen can be seen in Figure 1. In this review, patients were excluded if there was evidence of deep tissue invasion by the fungus (i.e., fungal pneumonia, found in one patient) or if the fungi were found colonizing the airways only (found in two patients).

Standardized surgical techniques were performed for all the operations, and these are described elsewhere.\(^13\) Information on patient demographic characteristics, pretransplant diagnosis, transplant date and type, and immunosuppressive medications was obtained from medical charts. We also obtained information on fungal infections and antifungal therapy. Finally, we recorded the clinical course of the patients after transplantation.

All patients received postoperative immunosuppression with cyclosporine A (5 to 10 mg/kg/d) or tacrolimus (0.05 to 0.1 mg/kg/d), azathioprine (1 to 2 mg/kg/d) or mycophenolate mofetil (2 to 3 g/d), and corticosteroids (methylprednisolone, 125 mg q12h for the first 48 h, followed by prednisone, 20 mg/d). Prednisone treatment was tapered to 5 mg/d over the following year. Some patients received induction immunosuppression with rabbit antithymocyte globulin as part of a clinical trial or if renal insufficiency developed in the early postoperative period. Since January 1999, patients received a monoclonal interleukin 2-receptor antibody (daclizumab or basiliximab) as part of their induction immunosuppression (83 patients). Episodes of acute allograft rejection were treated with methylprednisolone, 500 mg/d for 3 days, followed by a 2-week oral prednisone taper.

All patients at risk for cytomegalovirus infection (positive donor or recipient serology) received prophylaxis with ganciclovir. All patients received *Pneumocystis carinii* prophylaxis indefinitely. Candida infection prophylaxis consisted of nystatin “swish and swallow” for the first 6 months after transplant. In addition, since January 1997, aerosolized amphotericin B (either liposomal or conventional) was administered for at least 2 weeks after transplant. Aerosolized amphotericin B lipid complex was administered as part of an ongoing study according to a standardized protocol.\(^7\) Vancomycin and ceftriaxone were administered for bacterial infection prophylaxis during the first 2 weeks after transplantation. In patients with septic lung disease, antibiotic choice was individualized and guided by pretransplant culture findings.

Patients underwent surveillance bronchoscopies at 1, 3, 6, 9, and 12 months after transplantation, or as clinical indications developed. Specimens were routinely examined for fungal infections.

Patient characteristics are reported by using descriptive statistics. The Kaplan-Meier method was used for estimation of survival, and the log-rank test was used for comparison of the survival in patients with and without mycetomas. We also used the Kaplan-Meier method and the log-rank test to compare the

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**Figure 1.** Light microscopy photograph of patient 8 in our series showing (top) low-power view of the cavity in the left upper corner, inflammatory debris adjacent to it, and the mycetoma in the right lower corner (hematoxylin-eosin, original × 100). Bottom: high-power view of the mycetoma showing the morphologic elements of the fungus, which are consistent with Aspergillus (hematoxylin-eosin, original × 300).
survival of patients with sarcoidosis without mycetomas to that of patients with mycetomas. All p values < 0.05 were considered significant. Statistical software was used for all analyses (SAS version 8; SAS Institute; Cary, NC).

**Results**

There were 16 heart/lung transplants, 142 bilateral lung transplants, 143 single lung transplants, and 2 living-related lobar transplants for a total of 303 transplant operations. The pretransplant diagnoses were as follows: COPD (143 patients, 47.2%), cystic fibrosis or bronchiectasis (69 patients, 22.8%), pulmonary fibrosis (34 patients, 11.2%), primary pulmonary hypertension (19 patients, 6.3%), sarcoidosis (13 patients, 4.3%), congenital heart disease (12 patients, 4.0%), and other (13 patients, 4.3%). The mean ± SD age was 45.7 ± 14.1 years; 150 of 303 patients (49.5%) were female.

Mycetomas were identified in the lungs of 9 of 303 patients (3.0%). Six patients required transplantation because of sarcoidosis; emphysema, aluminum pneumoconiosis, and pulmonary fibrosis were responsible for transplantation in one patient each. The mean age of these patients was 44.4 ± 10.1 years. Five patients were female (55.5%). Seven patients underwent bilateral lung transplantation, one patient underwent single lung transplantation, and one patient underwent heart/lung transplantation. Detailed information about these patients can be found in Table 1.

Mycetomas were identified in the lungs of 9 of 303 patients (3.0%). Six patients required transplantation because of sarcoidosis; emphysema, aluminum pneumoconiosis, and pulmonary fibrosis were responsible for transplantation in one patient each. The mean age of these patients was 44.4 ± 10.1 years. Five patients were female (55.5%). Seven patients underwent bilateral lung transplantation, one patient underwent single lung transplantation, and one patient underwent heart/lung transplantation. Detailed information about these patients can be found in Table 1.

Table 1—Characteristics and Outcome of Patients With Mycetomas

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, Yr/Gender</th>
<th>Diagnosis</th>
<th>Transplant Type, Date</th>
<th>Graft Survival, d</th>
<th>Chest Radiograph Showing Mycetomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/Male</td>
<td>Sarcoidosis</td>
<td>Heart/lung, 2/18/1995</td>
<td>20</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>48/Female</td>
<td>Sarcoidosis</td>
<td>Double, 1/23/1996</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>63/Male</td>
<td>Pulmonary fibrosis</td>
<td>Left, 12/4/1996</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>41/Male</td>
<td>Aluminum pneumoconiosis</td>
<td>Double, 12/21/1996</td>
<td>929</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>48/Female</td>
<td>Sarcoidosis</td>
<td>Double, 4/24/1997</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>52/Female</td>
<td>Sarcoidosis</td>
<td>Double, 10/8/1997</td>
<td>725</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>27/Female</td>
<td>Emphysema</td>
<td>Double, 12/2/1998</td>
<td>480</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>42/Male</td>
<td>Sarcoidosis</td>
<td>Double, 7/4/1999</td>
<td>525</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>37/Female</td>
<td>Sarcoidosis</td>
<td>Double, 8/20/1999</td>
<td>478</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Aspergillus fumigatus was present in the respiratory secretions of three patients after transplantation, and one of these patients (patient 7) had an anastomotic infection with Aspergillus, while Aspergillus niger was identified in the secretions of two patients. All patients received a short course of therapy with IV amphotericin B lipid complex (except for patient 1, who received conventional amphotericin B), followed by oral itraconazole, inhaled amphotericin B, or a combination of the two for an extended period. Itraconazole levels were monitored initially every month and subsequently every 3 months during the treatment course. Therapy was slowly tapered based on negative culture results and the absence of clinical or radiologic signs of infection. Details on the treatment of each patient can be found in Table 2.

Eight patients survived their transplant operation. A fumigatus was present in the respiratory secretions of three patients after transplantation, and one of these patients (patient 7) had an anastomotic infection with Aspergillus, while Aspergillus niger was identified in the secretions of two patients. All patients received a short course of therapy with IV amphotericin B lipid complex (except for patient 1, who received conventional amphotericin B), followed by oral itraconazole, inhaled amphotericin B, or a combination of the two for an extended period. Itraconazole levels were monitored initially every month and subsequently every 3 months during the treatment course. Therapy was slowly tapered based on negative culture results and the absence of clinical or radiologic signs of infection. Details on the treatment of each patient can be found in Table 2.

The median survival after transplantation for the mycetoma group was 16 months (95% confidence interval, 0.5 to 31.0 months). The 1-year and 2-year survival rates were 55.5% and 14.3%, respectively. The survival of patients with mycetomas was significantly reduced compared to the 294 patients without mycetomas (median survival, 56.7 months; 95% confidence interval, 41.0 to 70.4 months; p = 0.0003). The 1-year and 2-year graft survival rates for this group were 77.9% and 68.9%, respectively. Figure 3 shows the survival curves of the two groups.

Four patients died in the first month after transplantation. Patient 5 died of presumed sepsis in the...
operating room, although intraoperative culture findings were negative and no causative organism was found at autopsy. The patient had received antifungal prophylaxis prior to lung transplantation with inhaled and IV amphotericin B and itraconazole, but pleural fluid and sputum culture performed 3 weeks prior to transplantation showed *A. fumigatus*. Patient 1, who had not received prophylaxis, died 20 days after heart/lung transplantation with evidence of invasive Aspergillus infection of the heart and lungs at autopsy. Patient 3 died 15 days after receiving a single lung transplant. The cause of death was ischemia reperfusion injury after transplantation, but *A. fumigatus* was present in BAL cultures. He had not received preoperative prophylactic antifungal therapy. Patient 5 died 8 days after transplantation because of renal failure in the setting of ischemia reperfusion injury.

Two patients died 17 months and 24 months after transplantation, respectively, without evidence of fungal infection. The first patient (patient 7) had chronic renal failure and a seizure disorder, while the second patient (patient 6) had chronic allograft dysfunction and died at home of unknown causes. Patient 4 required retransplantation for obliterative bronchiolitis 30 months after transplantation, and has had no problems with fungal infections 17 months after his second transplantation. He received 4 months of treatment with inhaled amphotericin B and itraconazole after his second transplantation. Finally, patients 8 and 9 are alive 17 months and 18 months, respectively, after transplantation with good allograft function; however, in patient 8, sarcoidosis has recurred in the transplanted lungs.

We also compared the survival of patients with mycetomas and the group of patients who underwent lung transplantation for sarcoidosis without having evidence of mycetomas in their explanted lungs (*n* = 7). The median survival for the seven patients who fulfilled these criteria was 18.0 months (confidence interval, 5.8 to 35.7 months). Their 1-year and 2-year survival rates were 71.4% and 42.9%, respectively. Their survival was not statistically different compared to that in the patients with mycetomas, but the numbers in each group were very small (*p* = 0.4727).

**Discussion**

The presence of mycetomas in the lungs of patients undergoing lung transplantation is predictive of a poor posttransplant outcome. Mycetomas were not very common in our transplant population, despite a relatively higher rate of diagnosis of sarcoid compared to that of the International Registry (4.3% vs 1 to 2%, respectively). Early posttransplant death was very common in this series, but invasive fungal infection was the cause of death in only one patient. Therefore, it is possible that mycetomas do not directly cause death, but they might identify patients at risk for perioperative complications.

Aggressive prophylaxis prior to transplantation was used in four of five patients who survived beyond the first month. In contrast, it was administered to only two of four patients who died early after transplantation. Two of the three patients who received no antifungal therapy prior to transplantation had mycetomas found unexpectedly in their explanted lungs. The third patient, whose case has been described previously, was the first person with mycetomas to undergo lung or heart/lung transplantation in our institution, and the importance of prophylaxis was not appreciated. Antifungal therapy prior to
transplantation cannot generally eliminate the mycetomas, and patients are too sick to undergo resection of the mycetomas. However, through early prophylaxis, the burden of fungal organisms might be decreased, therefore minimizing the likelihood of infection at the time of transplantation, when patients are severely immunosuppressed.

The removal of the diseased lungs during transplantation removes most of the fungal organisms, but enough may remain in the trachea and the proximal bronchi to cause disease. Furthermore, single lung transplantation is unable to achieve adequate removal of fungal organisms and should probably not be used in patients with mycetomas. The sole single lung transplant recipient in our series died of ischemia reperfusion injury, but Aspergillus was grown from BAL fluid prior to his death. Our present approach is to consider mycetomas as a form of suppurative lung disease and to treat patients with bilateral lung transplantation.

Our study also highlights the importance of careful screening for mycetomas by chest radiography and chest CT prior to transplantation to identify patients at high risk after transplantation. The utility of chest CT in pretransplant screening is controversial but should be employed in any patient with suspected mycetoma. In addition, fungal cultures where mycetomas are suspected could help identify the fungi and direct treatment. Finally, although sarcoidosis remains the most common diagnosis of patients with mycetomas, our series demonstrates their presence in patients with other end-stage lung diseases. Native lung disease cannot be used to exclude the possibility of mycetomas.

Antifungal therapy was well tolerated by the survivors, and it was very effective in minimizing positive fungal culture findings. Only one of five survivors beyond 1 month had a positive culture finding for *A. fumigatus*, and two survivors had *A. niger*. The lipid form of amphotericin B was generally employed for systemic and inhaled therapy. As an inhalational agent, our pilot data suggest liposomal amphotericin B is better tolerated than conventional amphotericin B and is at least as effective. In addition, the IV form achieves good tissue penetration and has less nephrotoxicity.

### Table 2—Pretransplant and Posttransplant Culture Results of Patients With Mycetomas*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Pretransplant Culture Findings</th>
<th>Pretransplant Treatment</th>
<th>Posttransplant Culture Findings</th>
<th>Posttransplant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>A. fumigatus</em> (BAL)</td>
<td>None</td>
<td>Aspergillus (autopsy heart/lungs)</td>
<td>ABIV, 3 wk; ITRA, 1 wk</td>
</tr>
<tr>
<td>2</td>
<td><em>A. fumigatus</em> (sputum)</td>
<td>ABIH, 2 mo; ITRA, 6 mo</td>
<td>None</td>
<td>ABIV, 1 wk</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>ABIH, 1 mo; ITRA, 16 mo</td>
<td><em>A. fumigatus</em> (BAL)</td>
<td>ABIV, 2 wk; ABIH, 2 wk</td>
</tr>
<tr>
<td>4</td>
<td><em>A. fumigatus</em> (BAL)</td>
<td>ABIV, 0.5 mo; ABIH, 0.5 mo; ITRA, 1 mo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td><em>A. fumigatus</em> (BAL/pleural fluid)</td>
<td>ABIH, 14 mo; ITRA, 7 mo</td>
<td>None</td>
<td>ABIV, 1 wk; ABIH, 8 mo; ITRA, 3 wk</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>None</td>
<td><em>A. fumigatus</em> (BAL)</td>
<td>ABIV, 4 wk; ABIH, 6 mo</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>None</td>
<td><em>A. fumigatus</em> (BAL)</td>
<td>ABIV, 1 mo; ABIH, 12 mo; ITRA, 14 mo</td>
</tr>
<tr>
<td>8</td>
<td><em>A. fumigatus</em> (sputum)</td>
<td>ABIH, 2 mo; ITRA, 5 mo</td>
<td><em>A. niger</em> (BAL)</td>
<td>ABIV, 2 wk; ABIH, 12 mo; ITRA, 12 mo</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
<td>ABIH, 9 mo; ITRA, 16 mo</td>
<td>None</td>
<td>ABIV, 2 wk; ABIH, 12 mo; ITRA, 12 mo</td>
</tr>
</tbody>
</table>

*ABIH = inhaled amphotericin B; ABIV = IV amphotericin B; ITRA = itraconazole.

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Figure 3. Comparison of patient survival between patients with and without mycetomas. X-axis = survival in years; Y-axis = percent survival. At the bottom of the graph, the number of patients in each group for different time points is given. Patients alive at the time of the analysis are censored (represented by circles).
rototoxicity compared to the conventional amphotericin B, which is very important in the setting of the other concomitant nephrotoxic medications that lung transplant patients receive.\textsuperscript{17–19} We hypothesize that our use of inhaled and systemic use of amphotericin B and prolonged azole therapy, with aggressive monitoring of itraconazole levels, all contributed to the low incidence of positive fungal culture findings after transplantation in these patients.

The scarcity of donor organs and the decreased survival of the patients in our series suggest that lung transplantation in patients with mycetomas should be re-examined very carefully. However, in patients receiving aggressive prophylaxis (unlike patient 1) and having limited disease (unlike patient 5, who had Aspergillus in the pleura), acceptable posttransplant survival was achieved. The implementation of these factors in our program was significant: no patient with mycetomas died in the first month after transplant since April 1997. We believe that lung transplantation should be pursued in these patients but with very careful selection of patients (avoiding patients with other comorbidities or with evidence of disseminated disease). Our sarcoid patients without mycetomas had higher survival rates than patients with mycetomas (although their survival was lower compared to the rest of the patients), but the difference was not statistically significant. However, even moderate survival differences could not be detected in our series because of small number of patients. Additional studies are needed in order to assess the relative impact of native lung disease and the presence of mycetomas on posttransplant survival.

Our study has certain limitations. The most important limitation is the number of patients. There were only nine patients with mycetomas and seven patients with sarcoidosis without mycetomas. Conclusions based on these small numbers may be wrong; therefore, our results should be used to generate hypotheses for larger studies. In addition, the retrospective nature of the study makes it possible that mycetomas were missed in some patients. However, this is unlikely because pulmonary pathology studies are very meticulous on identifying any lesions in the explanted lungs of transplant recipients. Finally, our approach to pretransplant and posttransplant management of mycetomas changed as more information and alternative treatment agents became available. Patients who received transplants after April 1997 appear to have done better compared to the first five patients with mycetomas who underwent transplantation; therefore, this report might not reflect outcomes with our current aggressive prophylactic and treatment practices.

In conclusion, patients with mycetomas undergoing lung transplantation appear to have worse outcomes compared with patients without mycetomas. Potential explanations for the decreased survival include fungal infections related to mycetomas, very advanced lung disease prior to transplantation (mycetomas might be markers), or pretransplant diagnosis. In the latter, patients with mycetomas often have sarcoidosis, a disease with worse survival after lung transplantation. Because some deaths appear related to infectious complications, aggressive diagnosis and antifungal therapy in these patients might lead to improved outcomes for this high-risk group. At this time, the presence of mycetomas should not be considered an absolute contraindication to lung transplantation, but patients with extensive disease should not undergo lung transplantation. Only a multicenter review of survival of patients with mycetomas and patients with sarcoidosis without mycetomas will have enough power to assess the true effect of mycetomas in these patients.

\textbf{References}