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To cite this version:
Nadim Cassir, Robin Delacroix, Carine Gomez, Veronique Secq, Martine Reynaud-Gaubert, et al.. Transplanted lungs and the “white plague” A case-report and review of the literature. Medicine, Lippincott, Williams & Wilkins, 2017, 96 (13), pp.e6173. 10.1097/MD.0000000000006173. hal-01521232

HAL Id: hal-01521232
https://hal.archives-ouvertes.fr/hal-01521232
Submitted on 1 Jun 2018

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Transplanted lungs and the “white plague”
A case-report and review of the literature

Nadim Cassir, MD, PhD, Robin Delacroix, Pharm. Resident, Carine Gomez, MD, Véronique Secq, MD, Martine Reynaud-Gaubert, MD, PhD, Pascal-Alexandre Thomas, MD, PhD, Laurent Papazian, MD, Nadim Cassir, MD, PhD, Robin Delacroix, Pharm. Resident, Carine Gomez, MD

Abstract
Rationale: Solid organ transplant recipients, especially after lung transplantation, are at increased risk for Mycobacterium tuberculosis pulmonary tuberculosis due to lifelong immunosuppression.

Patient concerns: A 41-year-old woman underwent a second bilateral lung transplantation that was complicated by fatal pulmonary tuberculosis.

Diagnoses: Histological examination of a lung biopsy performed 6 weeks after retransplantation revealed a caseating granuloma and necrosis. Acid-fast bacilli were identified as rifampicin-susceptible *M. tuberculosis* by real-time polymerase chain reaction (PCR), confirmed by culture 2 weeks later.

Interventions: Our investigation led us to highly suspect that the transplanted lungs were the source of *M. tuberculosis* transmission.

Lessons: In order to optimize diagnosis and treatment for lung recipients with latent or active tuberculosis, regular assessment of lower respiratory samples for *M. tuberculosis*, particularly during the 12-month period posttransplant should be implemented. Regarding donor-derived transmission, screening donor grafts with latent tuberculosis by *M. tuberculosis* real-time PCR in lymphoid and adipose tissues is an option that should be considered.

Abbreviations: BAL = bronchoalveolar lavage, CT = chest-computed tomography, DNA = deoxyribonucleic acid, IGRA = interferon-γ release assay, LTBI = latent tuberculosis infection, PCR = polymerase chain reaction, SOT = solid organ transplant, TST = tuberculin skin test.

Keywords: case-report, immunosuppression, lung, *Mycobacterium tuberculosis*, transplantation, tuberculosis

1. Introduction
Solid organ transplant (SOT) recipients are at increased risk for *Mycobacterium tuberculosis* pulmonary tuberculosis due to lifelong immunosuppression. In low tuberculosis-prevalence regions, the frequency of pulmonary tuberculosis in SOT recipients varies from 1.2% to 6.5%.[2] In this population, diagnosis delay, treatment-related toxicities, and drug interactions complicate the management of tuberculosis, leading to a up to 30% mortality.[1] Posttransplantation tuberculosis may result from reactivating latent tuberculosis in the recipient or transmission of *M. tuberculosis* from a contagious person or from the transplant.[1] Risk for pulmonary tuberculosis is greater for lung transplant receivers compared with other SOT recipients.[3] In this population, the onset of pulmonary tuberculosis varies from 1 day to 12 months after lung transplantation.[4–5]

In our hospital, diagnosing deadly pulmonary tuberculosis 8 weeks after bilateral lung transplantation led to investigate the source of *M. tuberculosis*. This case is reported anonymously in agreement with the advice n°2016–024 of the Méditerranée Infection Institute Ethics Committee.

2. Case report
A 41-year-old Caucasian woman underwent a primary double lung transplantation for cystic fibrosis in 2006. Her medical history was otherwise unremarkable and the patient had no known history of pulmonary tuberculosis or tuberculosis contact. On December 2015, she underwent retransplantation for chronic lung allograft dysfunction. During the month preceding retransplantation, 4 sputum specimens remained negative for acid-fast bacilli and specific *M. tuberculosis* culture and real-time polymerase chain reaction (PCR) testing. On postoperative day 42, deterioration of her respiratory status prompted a chest-computed tomography (CT) scan revealing sub-centimeter bilateral nodules primarily located in the
the patient was M. tuberculosis positive by real-time PCR. On postoperative day 62, Tuberculin skin test (TST) or interferon-γ release assay (IGRA) test were not performed. All the BALs performed on postoperative period yielded no other pathogen except for the one performed on day 60 that cultured Pseudomonas aeruginosa; the adjunctive antibiotic therapy was imipenem-cilastatin, 3g/d. Histological examination of a lung biopsy performed 6 weeks after retransplantation revealed a caseating granuloma and necrosis. Acid-fast bacilli were identified as rifampicin-susceptible M. tuberculosis by real-time PCR. On postoperative day 65, the patient’s status worsened with severe hypoxemia, shock unresponsive to high dose catecholamines, and multigorgan failure. The patient died on postoperative day 70, despite treatment combining isoniazid, rifampicin, ethambutol, and pyrazinamide. Retrospective real-time PCR testing of the explanted lung and BALs performed on postoperative days 1, 7, and 21 remained negative.

The organ donor died of posttraumatic intracerebral hemorrhage. He was a 47-year-old man with no history of lung disease or risk factors for tuberculosis other than chronic alcohol use and smoking. TST results were not available. During hospitalization, a lung CT-scan showed no signs of active or previous tuberculosis and no TST or IGRA test results were available. Routine cultures of per-transplantation right lung biopsy yielded Candida albicans. Retrospective M. tuberculosis real-time PCR yielded negative results on the left and right donor-lung biopsies. Both kidneys from the same donor were transplanted into 2 other recipients. Six months after transplantation, neither of the kidney recipients had developed any signs or symptoms suggestive of active tuberculosis.

3. Discussion

Several lines of evidence indicate that the transplanted lungs were the source of fatal pulmonary tuberculosis in the patient who underwent a second bilateral lung transplantation. During her 9-year history of her first bilateral lung transplant, the recipient had no known history of tuberculosis. In the month prior to second transplantation, she presented no clinical, CT-scan, or microbiological evidence of pulmonary tuberculosis. During regular monitoring, the first positive respiratory sample tested positive for M. tuberculosis was obtained 42 days after the second transplantation, while immunosuppressive therapy had been administered for 9 years following the first transplantation. Investigations found no evidence of a new infection posttransplant via healthcare-associated cross-transmission that could otherwise have explained this case. No case of active tuberculosis infection was diagnosed among her relatives, other patients or healthcare workers during the 3-month pretransplant period and the posttransplant stay in the thoracic surgery ward or intensive care unit.

A donor-to-recipient lung transmission was suspected in 15 cases of pulmonary tuberculosis in lung transplant recipients since 1990 (Table 1). It was conclusive in only 1 case reporting a 14-year-old girl with chronic bronchiectasis who was TST-negative before transplantation. She received a bilateral lung transplant from a 51-year-old man born in the Philippines with a solitary pulmonary nodule that was found on perioperative palpation. Histologic analysis of this nodule indicated a caseating granuloma and necrosis with positive AFB staining and the recipient BAL performed on postoperative day 3 was positive for M. tuberculosis by PCR and culture. Early initiation of antituberculosis treatment and the omission of induction immunosuppressive therapy led to a favorable outcome.

Current US and European guidelines recommend routine screening and treatment for latent tuberculosis infection (LTBI) in lung recipients but there is no controlled trial. Assessing LTBI includes reviewing epidemiologic risk factors, chest radiography and a TST and/or IGRA. However, TSTs and IGRA s are less sensitive in immunosuppressed and/or critically ill patients than in the general population and they do not differentiate LTBI from active tuberculosis.

There is no controlled trial to support specific recommendations regarding lung donors. One option would be to screen lungs just before or at the time of transplantation as early antituberculous treatment and immunosuppression optimization are essential to successfully treat lung recipients with active tuberculosis. In the case reported here, negative retrospective detection was obtained on fixed rather than fresh biopsies. TST or IGRA testing in deceased donors is difficult to perform and to interpret. Because M. tuberculosis DNA is detected in lymphoid and adipose tissues surrounding the lungs in LTBI patients, the cost-effectiveness of rapid real-time PCR testing of the donor lungs has to be evaluated in various tuberculosis prevalence settings.
<table>
<thead>
<tr>
<th>Recipient characteristics</th>
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<th>Microbiological results in the recipient</th>
<th>Delay from transplantation to diagnosis</th>
<th>Treatment/Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-y-old woman/heart-lung/pulmonary arterial hypertension/TST negative before transplant</td>
<td>N.A.</td>
<td>BAL samples showed AFB and culture yielded M. tuberculosis</td>
<td>4 mo</td>
<td>N.A./Died</td>
<td>Carlsen and Berger[6]</td>
</tr>
<tr>
<td>A 57-y-old woman/bilateral lung/chronic obstructive pulmonary disease/TST negative before transplant</td>
<td>45-y-old woman</td>
<td>BAL samples showed AFB which were identified as M. tuberculosis by DNA probe and confirmed by culture</td>
<td>3 mo</td>
<td>Isoniazid, ethambutol and pyrazinamide/ died</td>
<td>Miller et al[7]</td>
</tr>
<tr>
<td>42-y-old woman/single lung/end-stage chronic obstructive pulmonary disease</td>
<td>Normal chest radiograph and no known prior history of M. tuberculosis</td>
<td>BAL samples yielded M. tuberculosis—BAL showed AFB and cultures yielded M. tuberculosis</td>
<td>6 wk—idem</td>
<td>Isoniazid, ethambutol, and pyrazinamide/ improved</td>
<td>Ridgeway et al[8]</td>
</tr>
<tr>
<td>63-y-old woman/single lung/end-stage chronic obstructive pulmonary disease</td>
<td>Infection</td>
<td>DNA fingerprints of both M. tuberculosis isolates were identical</td>
<td>idem</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td>A 27-y-old man/bilateral lung/cystic fibrosis</td>
<td>19-y-old New York City resident</td>
<td>Lung biopsy specimens showed granulomatous inflammation with stainable AFB that yielded M. tuberculosis</td>
<td>3 mo—idem</td>
<td>Isoniazid, ethambutol, pyrazinamide, and streptomycin during 3 mo, followed by 15 mo of isoniazid and ethambutol/improved</td>
<td>Schulman et al[9]</td>
</tr>
<tr>
<td>A 57-y-old man/bilateral lung/idiopathic bronchiectasis</td>
<td>25-y-old South American man who had immigrated to New York City 2 y earlier</td>
<td>BAL samples showed AFB and culture yielded M. tuberculosis. Lung biopsy showed necrotizing granulomas</td>
<td>—</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td>35-y-old woman/bilateral lung/end-stage pulmonary lymphangioleiomyomatosis/TST negative before transplant</td>
<td>51-y-old, non-smoking, recent immigrant from China</td>
<td>Lung biopsy specimens showed granulomatous inflammation with stainable AFB that yielded XDR M. tuberculosis</td>
<td>5 mo</td>
<td>Isoniazid, rifampicin, pyrazinamide, and ethambutol replaced by levofloxacin, profeniamide, and cycloserine together with para aminosalicylic acid (PAS)/ improved</td>
<td>Lee (2003)</td>
</tr>
<tr>
<td>49-y-old woman/previous single lung transplant/ idiopathic pulmonary fibrosis/end-stage bronchiolitis/bilateral sequential lung retransplantation</td>
<td>Chest radiography with previously unnoticed pulmonary opacity</td>
<td>BAL samples yielded M. tuberculosis</td>
<td>1 d</td>
<td>Isoniazid, pyrazinamide, and levofloxacin/ improved</td>
<td>Winthrop et al[5]</td>
</tr>
<tr>
<td>28-y-old woman/heart-lung/pulmonary hypertension and restrictive cardiomyopathy</td>
<td>42-y-old man</td>
<td>BAL samples showed AFB and culture yielded M. tuberculosis. Lung biopsy disclosed necrotizing granulomas positive for AFB</td>
<td>2.5 mo</td>
<td>Isoniazid, rifampicin, pyrazinamide, and ethambutol/improved</td>
<td>Place (2007)</td>
</tr>
<tr>
<td>16-y-old boy/heart-lung transplant/pulmonary arterial hypertension</td>
<td>Contact with a patient with active tuberculosis for at least 1 y</td>
<td>BAL samples culture yielded XDR M. tuberculosis</td>
<td>2.5 mo</td>
<td>Ethambutol, ciprofloxacin, clarithromycin/improved</td>
<td>Shitrit et al[12]</td>
</tr>
<tr>
<td>68-y-old man/single-lung/coal worker’s pneumoconiosis/TST negative before transplant</td>
<td>30-y-old man, emigrated from Peru 11 y before/TST positive at 24 mm without LTBI prophylaxis</td>
<td>Cultures from the pericardium and the BAL yielded M. tuberculosis</td>
<td>3 mo</td>
<td>Ethambutol, isoniazid, pyrazinamide, and ciprofloxacin/died</td>
<td>Boedefeld et al[13]</td>
</tr>
<tr>
<td>60-y-old woman/single lung/idiopathic pulmonary fibrosis/TST negative before transplant</td>
<td>20-y-old man born in Mexico</td>
<td>Genotyping analysis of the strain revealed similarity with a cluster of patients from Mexico</td>
<td>5 mo</td>
<td>Rifampin, isoniazid, pyrazinamide, and ethambutol during 3 mo followed by rifabutin and isoniazid/related death</td>
<td>Mortensen et al[14]</td>
</tr>
<tr>
<td>(continued)</td>
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<tr>
<td>50-y-old woman/bilateral lung/TST negative before transplant</td>
<td>20-y-old man born in the USA, incarcerated 1 y before</td>
<td>BAL samples showed AFB and culture yielded <em>M. tuberculosis</em></td>
<td>2 mo</td>
<td>Rifampin, isoniazid, ethambutol, and pyrazinamide/N.A.</td>
<td>Mortensen et al(^{[14]})</td>
</tr>
<tr>
<td>50-y-old woman/bilateral lung/TST negative before transplant</td>
<td>20-y-old man born in the USA, traveled during 1 y just before donation in the Philippines</td>
<td>BAL samples showed AFB and culture yielded <em>M. tuberculosis</em></td>
<td>3 mo</td>
<td>Rifampin, isoniazid, ethambutol, and pyrazinamide during 2 mo, followed by 7 mo of rifampin and isoniazid/N.A.</td>
<td>Mortensen et al(^{[14]})</td>
</tr>
<tr>
<td>14-y-old girl/bilateral lung/idiopathic bronchiectasis/TST negative before transplant</td>
<td>51-y-old man born in the Philippines/histologic analysis of a nodule from the donor graft indicated a granuloma with caseation and necrosis with positive AFB staining</td>
<td>BAL samples were positive for <em>M. tuberculosis</em> by PCR and culture yielded <em>M. tuberculosis</em></td>
<td>5 d</td>
<td>Moxifloxacin, isoniazid, ethambutol, and pyrazinamide during 2 mo, followed by 10 mo of moxifloxacin, isoniazid, and ethambutol/improved</td>
<td>Nizami et al(^{[15]})</td>
</tr>
<tr>
<td>41-y-old woman/previous bilateral lung transplant/ cystic fibrosis/end-stage bronchiolitis obliterans/bilateral lung retransplantation</td>
<td>47-y-old, smoking, chronic alcohol user</td>
<td>Lung biopsy yielded granuloma with caseation and necrosis, AFB were identified as rifampin-susceptible <em>M. tuberculosis</em> by real-time PCR</td>
<td>8 wk</td>
<td>Rifampin, isoniazid, ethambutol, and pyrazinamide/died</td>
<td>This case</td>
</tr>
</tbody>
</table>

4. Conclusion
Given the substantial morbidity and mortality associated with active tuberculosis in lung recipients, it is crucial to come up with an early diagnosis for those with latent or active tuberculosis in order to optimize their treatment. Regular assessment of lower respiratory samples for *M. tuberculosis*, particularly during the 12-month period posttransplant should be implemented. Regarding donor-derived transmission, screening donor grafts with LTBI by *M. tuberculosis* real-time PCR in lymphoid and adipose tissues is an option that should be considered.

References