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Successful lung transplantation for chronic *Mycobacterium abscessus* infection in advanced cystic fibrosis, a case series

Lung allograft for CF with *M. abscessus*

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Abstract

Pulmonary *Mycobacterium abscessus* infection in cystic fibrosis (CF) patients is difficult to treat and considered a contra-indication for lung transplantation in most centers. We present four CF patients with chronic pulmonary *M. abscessus* infection, in whom lung transplantation was performed. Through intensive treatment before transplantation, we achieved control of the infection in all but one patient. After a mean of 16 months of follow up, three patients are doing well, without evidence of local or disseminated recurrence. One patient died early post-transplant due to an unrelated cause. These findings support the possibility of lung transplantation with favorable outcome in CF patients with *M. abscessus* infection.

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Introduction

Mycobacterium abscessus, a rapidly growing nontuberculous mycobacterium (NTM) inherently resistant to most classes of antibiotics, is an emerging pathogen in cystic fibrosis (CF). Pulmonary *M. abscessus* infections are a major concern in CF as they are associated with accelerated decline in pulmonary function and are notoriously difficult to treat¹. Furthermore, treatment side effects are numerous and managing them can be challenging.

In line with published guidelines², most centers consider pulmonary *M. abscessus* infection in CF an absolute contra-indication for lung transplantation. However, this view is being challenged³. In the present case series, we describe our experience with lung transplantation for end-stage CF in four patients with chronic pulmonary *M. abscessus* infection.

Methods

We retrospectively reviewed data of all CF patients transplanted in our center since January 2010. Patients who met the ATS/IDSA criteria for *M. abscessus* pulmonary disease⁴ and received treatment for *M. abscessus* infection prior to transplantation were included. All study patients had end-stage lung disease: all were oxygen dependent and using nocturnal non-invasive ventilation. All had received *M. abscessus* directed therapy in the past. Demographic, clinical, microbiology, treatment and outcome data were extracted from medical records. Mycobacterial culture was performed using NALC-NaOH decontamination and incubation in Bactec MGIT 960/320 (BD, Sparks, MD, USA) for six weeks. Species were identified via target detection in 16S-23S rRNA spacer region for *Mycobacterium spp.* / *M. tuberculosis complex*; 16S rRNA sequencing for NTM species determination.

The aim of antibiotic therapy was stabilization of the clinical condition with resolution of fever and major reduction in mycobacterial load prior to transplantation, i.e. at least three negative sputum smears and/or negative mycobacterial PCR, with ideally also sputum culture conversion for *M. abscessus*. Sputum culture conversion was defined as three consecutive negative mycobacterial

cultures from sputum and/or negative mycobacterial cultures from broncho-alveolar lavage (BAL) at explant.

Recipient and donor selection criteria and management have been described previously⁵ and have not changed over time with respect to *M. abscessus* infection. Standard induction and maintenance immunosuppression was given regardless of NTM infection⁵. After pneumonectomy of the explant lung, the pleural cavity and surgical incision of every recipient is thoroughly rinsed and mechanically brushed with a povidone-iodine antiseptic solution. In patients infected with *M. abscessus* this was done even more rigorously and repeated three to four times. There were no other differences in surgical technique. Surveillance bronchoscopy is routinely done on post-operative day 1, 90, 180, 360, 540 and 720 and at discharge after transplantation. All patients provided written informed consent for use of routinely collected data prior to transplantation.

Case reports (table 1)

Case 1

A 33-year-old male CF patient (F508del/F508del) was referred for combined lung-liver transplantation. *M. abscessus subspecies abscessus* was first isolated five months prior. Treatment consisting of intravenous ceftazidime, meropenem and amikacin, combined with oral linezolid and azithromycin, was started a month before referral. Because of relapse of fever, linezolid was replaced by moxifloxacin. He underwent a combined double-lung and liver transplantation two months after referral. Sputum culture conversion occurred two months prior to transplantation and cultures of the explant lungs were negative. The intravenous therapy was continued immediately post-transplant for three weeks, followed by a switch to an all-oral regimen consisting of moxifloxacin, azithromycin and inhaled amikacin, until six months post-surgery. Post-operative broncho-alveolar lavage (BAL) and sputum cultures remain free of *M. abscessus*. He is well 28 months post-transplant.

Case 2

A 20-year-old female CF patient (F508del/F508del) was referred for lung transplantation. She had been chronically infected with *M. abscessus subsp. bolletii* for seven years. Several eradication trials had failed. In preparation of transplantation, *M. abscessus* treatment was restarted with intravenous meropenem and amikacin, and oral moxifloxacin, doxycycline and azithromycin. After one month, because of side effects, meropenem was replaced by linezolid, and amikacin was switched to

inhalation. Five months after treatment initiation she underwent double-lung transplantation on central veno-arterial extracorporeal membrane oxygenation. Sputum culture converted four months before surgery; cultures of explant lungs were negative. Unfortunately, she died on the third postoperative day due to presumed bleeding at the aortic cannulation site, leading to exsanguination.

Case 3

A 21-year-old female CF patient (F508del/F508del), who had been chronically infected with *M. abscessus subsp. abscessus* for 16 months, was referred for lung transplantation. Salvage treatment for *M. abscessus* was started one month later: intravenous tigecycline and imipenem, with oral clofazimine, bedaquiline and azithromycin. Because of hepatotoxicity, bedaquiline and tigecycline were discontinued and replaced by linezolid and inhaled liposomal amikacin. She underwent double-lung transplantation three months following treatment initiation. Two months before transplantation sputum microscopy and mycobacterial PCR turned negative, cultures could at that point not be evaluated because of contamination. *M. abscessus* did not grow in cultures of the explant lungs. The same intensive therapy regimen – except for amikacin that was temporarily switched to intravenous – was continued after transplantation for three weeks. Subsequently, the continuation phase started, consisting of oral clofazimine, bedaquiline and azithromycin, and inhaled liposomal amikacin. Therapy was given post-operatively for 14 months. Post-operative BAL and sputum cultures remain free of *M. abscessus*. She is well 19 months post-transplant.

Case 4

A 40-year-old male CF patient (DF508/E528X), chronically infected with *M. abscessus subsp. bolletii* since three years, was referred for lung transplantation. Salvage treatment for *M. abscessus* was started three months after referral: intravenous tigecycline and imipenem, and oral clofazimine, clarithromycin and moxifloxacin. Because of unsatisfactory response, linezolid and intravenous amikacin were added after two months and bedaquiline was added ten days before transplantation. The patient underwent double-lung transplantation five months after treatment initiation. Sputum remained smear (rare acid-fast bacilli) and culture positive up until transplantation and BAL cultures of explant lungs were positive for *M. abscessus*. Because post-operative BAL also grew *M. abscessus*, tacrolimus target concentration was reduced. The intensive pre-transplant regimen was continued for 14 weeks post-surgery. Subsequently, an all-oral regimen of clofazimine, azithromycin, minocycline and linezolid was started. The patient continued therapy for 14 months post-

operatively. Cultures stayed positive four months post-transplant, but converted hereafter. He is well 16 months post-transplant.

Discussion

In the CF population chronic infection with *M. abscessus* is often associated with a faster and more progressive decline in lung function, even compared to chronic *P. aeruginosa* or non-*M. abscessus* NTM infection^{1,6}. This detrimental course, despite intensive antibiotic therapy, frequently leaves only one option, which is lung transplantation. Nevertheless, these patients are often considered not suitable as transplant candidates, based on early reports with dismal outcome due to post-operative skin, soft tissue or disseminated infection⁷⁻⁸. However, more recent reports⁹⁻¹⁰, have led to the belief that lung transplantation, with good outcome, is possible in CF patients with *M. abscessus* infection.

We report lung transplantation in four CF patients chronically infected with *M. abscessus*, with successful outcome in three of them. *M. abscessus* was first isolated a mean of 35 months (range 5-84) prior to transplant. Three patients received multiple *M. abscessus* directed antibiotic regimens (range 3-22), nonetheless general condition and lung function gradually declined. Case 1 received only one prior regimen, due to very rapid decline. Through intensive treatment regimens we achieved sputum culture conversion in three out of four patients prior to transplantation; the fourth converted four months post-transplant. There has been no evidence of local or disseminated disease following transplantation in any of our patients (follow-up 16-28 months). Treatment was in line with latest guidelines, except for the use of meropenem instead of recommended imipenem or cefoxitin in two patients⁴. The intensive treatment consisted of a combination of two to three intravenous, three or more oral, and one inhaled drug. The continuation phase consisted of an all-oral regimen of minimum three drugs.

We believe there are several reasons contributing to treatment success. First, our treatment was very intensive and aggressive. Therapy consisted of multiple IV drugs, combined from the start with oral drugs such as clofazimine and azithromycin as per most recent guidelines³. Second, the duration of the intensive phase was prolonged when possible to 12 weeks or until transplantation, whereas previous treatment regimens often only consisted of a two week IV therapy with one or two anti-mycobacterial drugs. We also included new or repurposed drugs to ensure enough 'effective' drugs. For example, clofazimine based on significant *in vitro* activity on *M. abscessus* and reported synergistic effects with amikacin¹¹; inhaled liposomal amikacin despite limited data for this indication¹²; and bedaquiline (off-label use in two patients) as an experimental drug based on

preliminary efficacy reports¹³. Last, given the precarious situation of the patients that were referred to us, therapy was started in-hospital and side-effects were meticulously followed up. Frequent sputum cultures were requested since it was crucial to demonstrate control of the infection, as to safely perform lung transplantation, reducing the risk of complications to a minimum.

When considering lung transplantation in patients with *M. abscessus* infection, it is thus strongly recommended to implement aggressive and prolonged antibiotic therapy in preparation of transplantation, in an attempt to control or even eradicate the infection. Our findings subscribe this recommendation. As *M. abscessus* infection in CF is mostly pulmonary, resection is able to remove the bulk of infection, especially when it is maximally suppressed by medical therapy. In addition, rigorous and repetitive rinsing of the pleural space and thoracotomy wound with an antiseptic solution is mandatory after removal of the native lung. To maximize success, treatment was continued immediately post-transplant in a two-phased approach. Given the high risk of dissemination of the infection post-surgery, immediately post-transplant drugs were given intravenously for a minimum of three weeks, combined with clofazimine as soon as possible. Subsequently, a continuation phase was started, consisting of an all-oral regimen of minimum three drugs, based on the appreciated effectiveness of the anti-mycobacterials pre-transplant. The importance of continued treatment is shown in case 4, in whom mycobacterial culture converted four months post-transplant. Although there is no evidence to support treatment duration, we believe treatment should be continued 12 months after culture conversion or transplantation, whichever occurred last, in line with guidelines⁴. Because of treatment side effects, toxicity and/or drug-drug interactions, this can be challenging, resulting in too early discontinuation as in case 1 and 4. There are no guidelines on immunosuppressive regimen after lung transplantation in these patients. Contrary to others³, we used standard induction and immunosuppression. Only in one case immunosuppression was reduced, after cultures became positive for *M. abscessus*.

Our data support previous reports that a favorable outcome, with clearance of *M. abscessus*, is possible when transplanting CF patients infected with *M. abscessus*. Three out of four patients are doing well at follow-up; the death of one was not attributed to *M. abscessus* infection. Although this is a single-center retrospective study, with a small number of patients, our findings are relevant to report in the context of this emerging and potentially devastating condition.

In conclusion, we suggest that *M. abscessus* infection in CF does not necessarily preclude lung transplantation, provided adequate mycobacterial load reduction has been obtained prior to surgery and optimal treatment is continued thereafter.

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Authors Contribution statement

N.L. was responsible for the study design. Data acquisition was largely done by D.R., a smaller part was collected by N.L. Analysis and interpretation of the data was done by N.L. and D.R., with the help of V.S., R.V., J.V.I., G.V., V.R.D. and L.D. D.R. and N.L. drafted the article, it was critically revised for important intellectual content by all authors: N.L., D.R., V.S., R.V., J.V.I., G.V., V.R.D. and L.D. All authors gave final approval of the version to be published.

Table 1: Pre-transplant characteristics, drug susceptibility and outcome

Case	CF-related comorbidity	BMI	FEV1 %pred at dg/LTx	Co-existing organisms	Mab drug susceptibility †	Treatment duration (m) ‡	Complications	FEV1 and FVC %pred at FU
1	diabetes, bronchiectasis, liver cirrhosis	16.5	22/19	S. marcescens	S: amikacin, clarithromycin	9	hearing loss	71/64
2	diabetes, bronchiectasis	19.2	65/37	S. apiospermum	R: amikacin, clarithromycin	5	tinnitus, nausea, vomiting	/
3	diabetes, bronchiectasis, liver fibrosis	14.9	40/15	P. aeruginosa, S. maltophilia, A. fumigatus	I: amikacin R: clarithromycin	17	hearing loss, nausea, vomiting, liver toxicity	107/105
4	diabetes, bronchiectasis	22.7	28/19	S. maltophilia, E. coli, A. xylosoxidans	I: amikacin, R: clarithromycin	18	nausea, vomiting, liver toxicity	91/111

BMI: body mass index (kg/m^2); CF: cystic fibrosis; dg: diagnosis; FEV1 %pred: percent predicted of forced expiratory volume in 1 second; FU: follow-up; FVC: forced vital capacity; I: intermediate; LTx: lung transplantation; m: months; Mab: *M. abscessus*; R: resistant; S: susceptible

†: drug susceptibility at start of salvage treatment

‡: total treatment duration from the start of the final intensive treatment pre-transplantation