# Lung transplantation: *Mycobacterium abscessus* as a cause of graft dysfunction

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Lung transplantation (LT) is a therapeutic option in patients with end-stage lung diseases where other effective treatments are lacking [1]. However, the procedure is not without risks and side-effects. One of the most important causes of morbidity and mortality in these patients is infection [1, 2]. Recently, there has been an increase in the incidence of emerging infections, with the majority of mycobacterial infections due to *Mycobacterium tuberculosis* [3], although this is not the only pathogen in the mycobacteria group. Atypical mycobacteria are also being identified with increasing frequency as the cause of disease in transplant patients [2, 4–7].

An increased incidence of nontuberculous mycobacteria (NTM) has been reported in LT recipients, particularly in cystic fibrosis (CF) [8]. In addition, the importance of NTM cultures prior to LT as a predictor of NTM infection and disease has been highlighted.

The aim of this case presentation is to review a particular variant of mycobacterial involvement in lung transplant patients, that is infection by *Mycobacterium abscessus*, by analysing the characteristics of the patients, the infection, the treatment options and the problems.

Between 1991 and 2005, a total of 286 lung transplants were performed at La Fe University Hospital (Valencia, Spain). Of these, 212 were double-lung, 49 single-lung, 24 heart-lung, and one was a liver-lung transplant. A retrospective descriptive study was carried out, in which a total of three cases of *M. abscessus* infection were observed.

NTM culture was considered positive when acid-alcohol resistant bacilli (AARB) were present in lung specimens, and they were subsequently identified as *M. abscessus*. The disease caused by NTM was diagnosed according to American Thoracic Society (ATS) guidelines [9], which include constitutional symptoms (cough, fever, chills, malaise), radiographic changes (new infiltrates, nodules), bacteriological criteria and positive culture, with or without evidence of granulomatous inflammation in the lung tissue.

All three patients were in a state of stable chronic rejection (bronchiolitis obliterans syndrome; BOS). All of them had forced expiratory volume in one second ($FEV_1$) deterioration and transbronchial biopsies with histological changes according to the definition of BOS [10, 11]. In all cases, other causes of graft dysfunction, such as infection, were ruled out. Case 2 was in BOS grade 1, and cases 1 and 3 were in BOS grade 2.

Patient characteristics are summarised in table 1.

**Table 1** *Characteristics of patients and M. abscessus infection*

| Case | Sex | Age yrs | Pre-LT BAL | LT type | Donor BAL | Disease | T time months | BOS | Site | Antibiogram (susceptible) | Antibiogram (resistant) | Treatment duration months | Follow-up NTM | Status | Survival after LT months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 57 | Negative | DL | *S. aureus* | Emphysema | 4 | 2 | BAL | Amikacin, erythromycin, linezolid, tobramycin | Ethambutol, isoniazid, rifampicin, streptomycin | 2 | 9 | Alive | 13 |
| 2 | Male | 20 | *S. aureus*<br>*P. aeruginosa* | DL | *S. aureus*<br>*E. coli*<br>*H. influenzae* | CF | 11 | 1 | BAL<br>Bone marrow<br>Blood | Amikacin, ciprofloxacin, erythromycin, linezolid | Ethambutol, isoniazid, levofloxacin, rifampicin | 3 | 14 | Alive | 25 |
| 3 | Female | 17 | MR<br>*P. aeruginosa* | DL | *S. aureus*<br>*H. influenzae* | CF | 26 | 2 | Subcutaneous and pulmonary nodules | Amikacin, gentamycin, tetracycline, tobramycin | Ethambutol, isoniazid, streptomycin, rifampicin | 5 | 15 | Dead | 41 |

*BAL: bronchoalveolar lavage; LT: lung transplantation; BOS: bronchiolitis obliterans syndrome before infection with nontuberculous mycobacteria (NTM); DL: sequential double lung; S. aureus: Staphylococcus aureus; P. aeruginosa: Pseudomonas aeruginosa; E. coli: Escherichia coli; H. influenzae: Haemophilus influenzae; MR: multiply resistant.*

## Case 1

Case 1 had a deterioration in lung function (forced vital capacity (FVC) 48.5% predicted, $FEV_1$ 44.3% predicted). Empirical treatment was initiated with broad-spectrum antibiotics (*i.v.* ceftazidime, teicoplanin and caspofungin) and corticosteroid boluses (*i.v.* methylprednisolone). The presence of rejection was ruled out by transbronchial biopsy, and corticosteroid boluses were discontinued. The presence of AARB was detected in the bronchoalveolar lavage (BAL) and these were subsequently identified as *M. abscessus*. The regimen was changed according to the antibiogram, instituting treatment with linezolid, amikacin and azithromycin. The patient showed clinical and functional improvement (figure 1). Two months later, the patient was rehospitalised owing to the side-effects of linezolid (diarrhoea, pancytopaenia and interaction with immunosuppression). BAL cultures were repeatedly negative for AARB and it was decided to discontinue treatment, with satisfactory progression of the patient. One year after lung transplantation, the patient was alive and free of NTM disease.

## Case 2

Case 2 presented with subcutaneous nodules from which *M. abscessus* was isolated (figure 2), followed by sepsis with involvement of the lung (BAL: AARB-positive and fall in $FEV_1$; figure 1), bone marrow and peripheral blood. Empirical treatment was instituted until an antibiogram was obtained, at which time the regimen was changed to linezolid plus ciprofloxacin. The patient had an indwelling Port-A-Cath® device, which acted as a reservoir of infection. Following its removal and antibiotic therapy, the patient progressed satisfactorily. In this case, side-effects of linezolid, including diarrhoea, nausea, vomiting, abdominal pain and interaction with immunosuppression, also occurred and required the replacement of linezolid with clarithromycin. Three months later, cultures were negative and treatment was discontinued without recurrence of the infection. After 2 years' follow-up, this patient was alive, in stable BOS grade 2 and without evidence of NTM disease or isolates.

## Case 3

Case 3 presented as subcutaneous nodules in the knees and pulmonary nodules on computed tomography (CT; figure 3), associated with a deterioration in lung function (figure 1). Biopsy of these nodules revealed the presence of AARB

identified as *M. abscessus*. Treatment was instituted according to an antibiogram with tetracycline, tobramycin and azithromycin. Cultures of the lesions were negative after 3 months and lung function recovered. The total duration of treatment was 5 months and no adverse reactions to treatment were observed. Patient 3 died 4 years after LT as a consequence of progressive graft deterioration with an established grade 3 BOS refractory to treatment and changes of inmunosuppression.

## Additional points

The 5-year survival experience in this centre in LT is almost 50%, although in CF, this rises to almost 60%.

All three cases reported here had respiratory fungal colonisation prior to *M. abscessus* infection. Cases 1 and 2 had colonisation by *Aspergillus* sp. In case 3, *Candida* sp. were isolated repeatedly in the months prior to *M. abscessus* infection. All patients had routinely received antifungal prophylaxis with endovenous fluconazol and inhalated caspofungin in the early postoperative LT period, and oral fluconazol after this period.

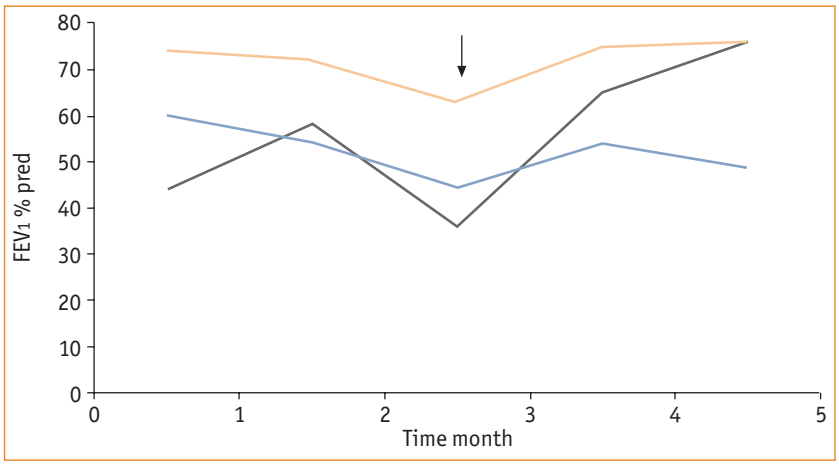
## Discussion

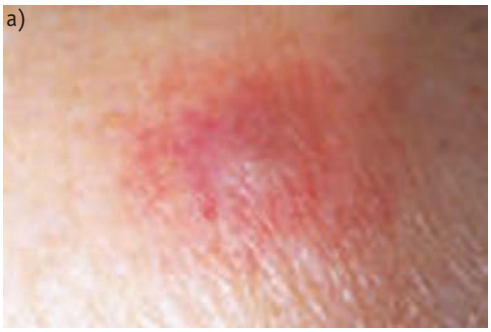
Mycobacterial infection in solid organ transplant recipients is a well known and documented occurrence [2–5]. MALOUF and GLANVILLE [2] have previously calculated an incidence of mycobacterial infection after lung transplantation of 9%, of which *M. abscessus* infection had an incidence of 1.14% (only three cases), a proportion coinciding with the three cases found in this study (1.04%).

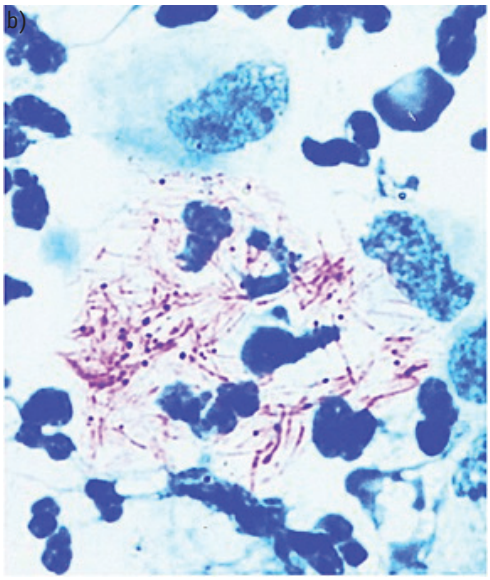
Some authors [2, 12] have raised the possibility that infection in the transplant patient may be due to transfer from the transplanted lung. However, as demonstrated by the negative BAL culture of the donors (table 1), this phenomenon was not observed here.

An alternative explanation for NTM infection in LT recipients is pre-LT colonisation by NTM, particularly *M. abscessus* in CF patients [8]. However, none of the three cases presented had NTM or AARB isolations in pre-operative studies before LT (table 1).

Like MALOUF and GLANVILLE [2] and PATEL *et al*. [13], in this series infection by *M. abscessus*, as well as by other NTM, occurred fairly late in the post-transplant period (4, 11 and 26 months post-transplant). However, unlike these authors, it was not found that patients with skin and subcutaneous tissue involvement had no graft



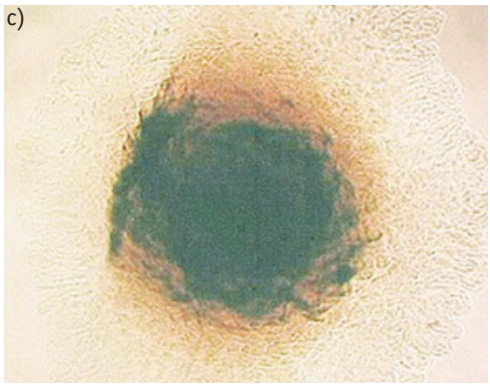
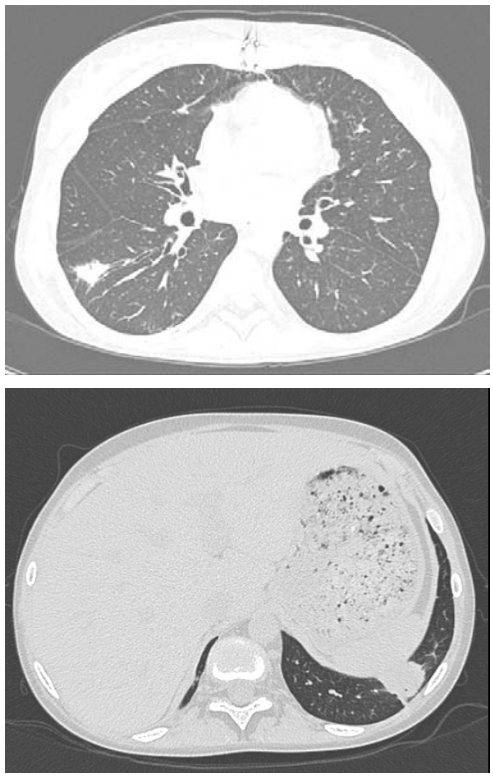




***Figure 1***
*Functional improvement after treatment in M. abscessus infection. Arrow indicates the time of diagnosis. Blue: case 1; orange: case 2; grey: case 3.*

***Figure 2***
*a) Subcutaneous nodule. b) Ziehl-Neelsen staining showing acid-alcohol resistant bacilli. c) Colonies with a creamy appearance in Lowenstein culture medium.*

***Figure 3***
*Pulmonary nodules on CT.*



dysfunction [2]. In two of the present cases, extrapulmonary involvement was associated with lung dysfunction. This is not a surprising observation, since extrapulmonary disease reflects a disseminated infection which obviously affects the lung.

As mentioned, all three patients were in chronic rejection (BOS). This term reflects graft deterioration due to a persistent airflow obstruction [10]. However, not all lung transplant recipients in whom airflow obstruction develops have BOS. Evaluation and treatment of other conditions, such as infection, that may alter graft function must be carried out before a diagnosis of BOS can be made.

It is also worth noting that all three patients had previously been colonised by different species of fungi (*Aspergillus* sp. and *Candida* sp.). This fact, in the context of chronic rejection (BOS), suggests that this possible co-infection by mycobacteria and fungi may be favoured by the inflammatory state of the airways, which would in turn facilitate colonisation and proliferation of opportunistic organisms. It was also found that this infection superimposed on existing BOS had a deleterious effect on lung function, which was reversible after eradication of *M. abscessus*.

In 1997, the ATS published a consensus statement on the diagnosis and treatment of disease caused by NTM, in which the criteria for diagnosis of NTM infection were established [9]. The fact that the current cases do not match all of these criteria could be interpreted as an absence of *M. abscessus* infection and thus be considered as colonisation. This aspect has also been discussed by CULLEN *et al*. [14]. However, the isolates of *M. abscessus* in the patients reported here were more likely to be due to infection than colonisation, because of the improvement in lung function and clinical symptoms seen after treatment.

Some authors consider that diagnosis of *M. abscessus* is difficult [15, 16]. In the present series, diagnosis was obtained by performing routine bacteriologocal examination and tests for monitoring and follow-up of transplant patients recommended by the Spanish Society of Pneumology and Thoracic Surgery guidelines for lung transplantation [1].

Although the LT series includes patients between 1991 and 2005, the three cases presented were collected in the last 4 years of the series. The fact that cases of *M. abscessus* infection have not been identified previously could be explained by the variation of isolation techniques and identification methods of NTM, resulting in an underestimation of the real prevalence of NTM in LT recipients in the study cohort.

Treatment is without a doubt the most controversial issue, both in terms of drug choice and duration of therapy. The different isolates of *M. abscessus* are systematically resistant to standard antituberculous drugs and generally susceptible only to parenteral antibiotics and the new oral macrolides [14].

Empirical treatments have been proposed consisting of clarithromycin (15–30 $mg \cdot kg^{-1}$, max. 1 $g \cdot day^{-1}$), amikacin (10–15 $mg \cdot kg^{-1}$, in two doses) and cefoxitin (200 $mg \cdot kg^{-1}$, max. 12 $g \cdot day^{-1}$), with a duration of 2–4 weeks until reception of the antibiogram [9, 17].

WALLACE *et al*. [18] reported that linezolid exhibited good activity against NTM, while noting that *M. abscessus* had the lowest susceptibility (23% of isolates had a minimum inhibitory concentration <8 $\mu g \cdot mL^{-1}$). However, in two of the present cases, *M. abscessus* was susceptible to linezolid and this drug was effective for treatment (table 1).

Other authors have provided data regarding susceptibilities to other drugs: clarithromycin (100%), amikacin (90%), cefoxitin (70%) and imipenem (50%) [9].

A treatment duration of at least 12 months after culture negativisation has been suggested, in combination with chronic suppressive therapy

(oral clarithromycin and aerosolised amikacin) [17]. Parenteral therapies with a 4–6 month duration have also been suggested [15]. In this study, a shorter 3–5 month duration of therapy until negative cultures were obtained did not result in any relapse of infection or clinical worsening in subsequent years of follow-up. The presence of adverse effects, particularly due to linezolid, was also a reason for shortening the duration of therapy.

Although specific treatment against *M. abscessus* was discontinued, azithromycin maintenance therapy was continued in doses of 250 mg·day$^{-1}$ three times per week, due to its stabilising effect on BOS [19]. This therapy would explain the maintenance of graft function seen and could be considered as a long-term eradicative therapy for *M. abscessus*, given the susceptibility of this organism to other orally administered macrolides (*e.g.* erythromycin). However, azithromycin was not tested in the antibiograms of the different mycobacteria. It also cannot be accurately determined whether azithromycin at that dose is effective for the eradication of atypical mycobacteria – here more complex studies with longer term follow-ups would be needed.

In conclusion, *M. abscessus* infection in LT patients is a relatively infrequent entity, which experience has shown had a benign course after institution of appropriate treatment. However, there is no room for complacency in immunosuppressed patients as such infections may still have a fatal outcome [20].

## Educational questions

1. Which are the most important causes of graft dysfunction in LT?
2. When a graft dysfunction is detected, which invesitigational studies should be performed?
3. What is the approximate incidence of NTM disease after lung transplantation?
4. What are the diagnostic criteria for NTM disease?
5. What is the most appropriate treatment for NTM, especially for *M. abscessus*? What should its duration be?
6. When can the term BOS be used? What are its consequences?

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## Suggested answers

1. The most important causes of graft dysfunction in LT are infections and rejection. In the early post-operative period, infections are usually caused by viruses and bacteria, and rejection is generally expressed as acute rejection until inmunosuppression is adjusted. In the late period, bacterial and fungal infections are more frequent, and BOS as an expression of chronic rejection is the most important in this period.
2. When a graft dysfunction is detected, all investigations are directed towards excluding infection and rejection. Cultures of peripheral blood, BAL and sputum are useful tools to detect infection. It is very important to carry out this comprehensive testing as there are many clinical signs that suggest rejection, such as fatigue, tachycardia or tachypnoea. Measurement of lung function is mandatory, and transbronchial biopsy is the best technique to exclude or confirm rejection.
3. The incidence of NTM infection in LT recipients ranges from ~9% [2], up to 13.7% in CF patients who have undergone LT [8].
4. The ATS published a consensus statement for the diagnosis of NTM that includes three criteria: 1) clinical signs and symptoms of cough, fever, fatigue, weight loss, haemoptysis and dyspnoea with exclusion of other disease; 2) findings on chest radiography (nodules and/or multifocal bronchiectasis); 3) bacteriological isolation of the NTM organism on sputum/bronchial washings or tissue biopsy [9].
5. *M. abscessus* is a virulent organism and is difficult to treat. Combination therapy is needed for *M. abscessus* until an antibiogram is available: clarithromycin (15–30 $mg \cdot kg^{-1}$, maximum dose of 1 $g \cdot day^{-1}$), amikacin (10–15 $mg \cdot kg^{-1}$ divided twice daily to achieve serum levels of 20 $\mu g \cdot mL^{-1}$) and cefoxitin (200 $mg \cdot kg^{-1}$, maximum dose of 12 $g \cdot day^{-1}$) for 2–4 weeks for empirical treatment pending sensitivities. Further recommendations for treatment include serial sputum cultures to assess response, and treatment for at least 12 months after cultures are negative, with longer treatment or chronic suppressive treatment if necessary [16]. However, in the authors experience, shorter treatment duration has been as effective as longer courses.
6. The term BOS reflects graft deterioration due to a persistent airflow obstruction caused by small airway destruction [10]. However, not all lung transplant recipients in whom airflow obstruction develops have BOS. A correct evaluation and treatment of other conditions, such as infection, that may alter graft function is necessary before a diagnosis of BOS can be made.