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CASE REPORT

Acute respiratory distress syndrome secondary to *Mycobacterium abscessus* lung infection – a case report

[version 1; peer review: 3 approved with reservations]

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Abstract

Mycobacterium abscessus (*M. abscessus*) is among the most common rapidly growing mycobacteria causing infections in humans. Skin and soft tissue infections, especially those following trauma or surgery are the most common infections caused by this pathogen. We describe the case of a 22-year old female with cerebral palsy and chronic respiratory insufficiency requiring nocturnal ventilation through a tracheostomy, who was admitted to a hospital with worsening shortness of breath, fever, and ventilator dependence. The patient was diagnosed with acute respiratory distress syndrome (ARDS) caused by bilateral pneumonia due to *M. abscessus* infection. The patient received prolonged antibiotic treatment and respiratory support which led to clinical recovery and bacteriological cure.

Open Peer Review

Approval Status ? ? ?

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version 1	?	?	?
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1. David E Griffith , University of Texas Health Sciences Center, Tyler, TX, USA 2. Hartmut Lode , Chest Hospital Heckeshom, Berlin, Germany 3. Michael Loebinger , Royal Brompton & Harefield Hospital Foundation Trust and Imperial College London, London, UK Steven Cowman , Imperial College London, London, UK			

Any reports and responses or comments on the article can be found at the end of the article.

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Case report

A 22 year old Hispanic woman who had a history of cerebral palsy, seizure disorder with tracheostomy and required night-time mechanical ventilation for chronic respiratory insufficiency, was admitted to the hospital with a gradually worsening shortness of breath, fever, chills and rigor that persisted over the course of 1 week.

The patient had been on assist control ventilation through a tracheostomy and portable home-ventilator (Pulmonetics LTV 1000; Carefusion Corp. San Diego, CA) for 12 months prior to this hospitalization. Although she had suffered from frequent respiratory tract infections in the past, with the last one being 4 months prior to this admission, she required mechanical ventilation only at night-time, as she breathed spontaneously during the day, and received feeding through a gastro-enterostomy tube. There was no previous history of seizures. The patient's family denied any recent weight loss, night sweats or skin rashes. Her home medications included levetiracetam 250 mg per G tube twice daily, multivitamins and inhaled albuterol as needed for bronchospasm. Her vital signs upon admission were as follows: blood pressure of 84/50 mmHg, heart rate of 109 beats per minute, respiratory rate of 20 breaths per minute, oral temperature 38.3°C, and oxygen saturation of 98%. Her home ventilatory setting included assist-control mode at a rate of 10/minute, tidal volume of 400 ml and positive end-expiratory pressure of 5 cm H₂O through a positive end-expiratory pressure (PEEP) valve built into the lambda ventilator circuit. She was immediately admitted to the intensive care unit (ICU).

Physical examination revealed a frail, non-verbal female with habitus and posture suggestive of spasticity, connected to a ventilator via tracheostomy. Physical examination of the chest revealed scattered crepitations over bibasilar lung fields, and predominantly over the right axillary area. She had severe spasticity affecting both the upper and lower extremities. Her initial chest X-ray showed a multifocal pneumonia predominantly confined to the right upper lobe. Admission labs revealed hemoglobin 12.5 gm/dL, white count $8.8 \times 10^3/L$, platelets $197 \times 10^3/L$. Her serum sodium levels were 138 mEq/dL, and the blood urea nitrogen (BUN) and creatinine values were 20 mg/dL and 0.9 mg/dL respectively. Arterial blood gas showed a pH of 7.30 and PaO₂ of 70 mmHg.

In addition to fluid resuscitation with normal saline infusions, given her history of pneumonia caused by *Pseudomonas aeruginosa* 3 months before the hospitalization, the patient was started on intravenous piperacillin and tazobactam at 3.75 g every 8 hours. Her blood cultures were drawn and were subsequently reported as negative for both bacterial and fungal organisms. Respiratory cultures obtained from tracheal aspirate grew *P. aeruginosa* sensitive to meropenem and hence she was started on meropenem 500 mg intravenously every 6 hours, after discontinuing piperacillin and tazobactam as well as vancomycin. Despite being on antibiotics for 7 days and showing negative culture for *Pseudomonas*, she continued to be febrile with temperature spikes of 38.6°C with night sweats. Oxygen saturation progressively worsened and subsequent chest X-rays showed a progressive increase in pulmonary infiltrates bilaterally, involving all four lung quadrants. Further laboratory cultures for respiratory

pathogens including a viral panel, *Legionella*, *Mycoplasma* and cocci serology were negative. Her sputum obtained from the tracheal aspirate grew *Mycobacterium abscessus*, initially identified as *M. chelonae-abscessus* complex, on day 10 of admission to the ICU. By this time, the patient showed a progressive decline in her respiratory status with computerized tomographic (CT) scans of the chest revealing findings consistent with a 'tree-in-bud' appearance on the initial images (Figure 1). Intravenous cefoxitin 2 g every 6 hours along with intravenous azithromycin 500 mg daily was started. Her progressive deterioration in respiratory status and worsening of the pulmonary infiltrates were consistent with acute respiratory distress syndrome (ARDS) characterized by bilateral four quadrant infiltrates and PaO₂/FiO₂ ratio <200 in the absence of features of left atrial hypertension (Figure 2). A 2D echocardiogram showed left ventricular ejection fraction of 65% without any evidence of atrial or ventricular dysfunction. The patient required a fractional inspired oxygen (FiO₂) concentration of 100%, PEEP of 10 cm H₂O, and low tidal volume ventilation with permissive hypercapnia. She then received low tidal volume "lung protective" ventilation keeping the tidal volume of 400 ml and careful fluid management to prevent fluid overload for the underlying ARDS. The patient was also maintained on respiratory support therapy including chest physical therapy and inhaled bronchodilators including albuterol.

On day 15 of hospital admission, the drug sensitivity report revealed that the infection was caused by a multidrug resistant *M. abscessus* strain, sensitive only to tigecycline and amikacin. Therefore the patient was started on intravenous (IV) tigecycline 50 mg twice daily and inhaled amikacin 500 mg twice daily. After being on these regimen for 7 days, there was a progressive improvement in

Figure 1. Axial CT of chest shows scattered tree-in-bud opacities (arrow head) in bilateral lower lobes. There is also a trace left pleural effusion.

Figure 2. Axial CT of chest shows multifocal airspace opacities including scattered areas of tree-in-bud opacities (arrow head). There are also bilateral small pleural effusions.

oxygenation and radiological evidence for resolution of pulmonary infiltrates. After a prolonged hospital stay for 6 weeks, the patient was subsequently discharged to a long-term acute care facility and inhaled amikacin for 4 weeks and IV tigecycline for a total of 12 weeks. Sputum cultures were repeated at the 8th and 12th week of treatment with tigecycline and revealed no mycobacterial growth ("bacteriological cure"). The patient's bacteriological cure from this atypical mycobacterium correlated with her clinico-radiological course, as evidenced by the improvement in the pulmonary infiltrates. A subsequent chest CT scan that was performed 8 weeks after commencement of tigecycline confirmed these findings (Figure 3). She returned to her home ventilator settings of assist-control mode with minimal oxygen requirements (fractional inspire oxygen of 30%). Subsequent outpatient follow-up at 3 months up revealed a stable cardiorespiratory status at her baseline.

Discussion

M. chelonae-abscessus complex, subspecies *abscessus* accounts for 85% of the pulmonary diseases caused by *M. chelonae* isolates¹. *M. abscessus* is a rapidly growing, aerobic acid fast bacillus (AFB) that produces non-pigmented colonies on most types of solid medium in less than 7 days². Although *M. abscessus* is a rapid grower, complete speciation of the organism is important but not often done in most clinical laboratory settings. Hence, *M. abscessus* is often confused with *M. chelonae*. The organism isolated from our patient was initially identified as *M. chelonae* but was subsequently confirmed as *M. abscessus*. This is important for several reasons as both organisms have different clinical manifestations. *M. chelonae* typically affects patients who are immunosuppressed and are on chronic steroid therapy. The majority of these patients present with disseminated skin and soft tissue infections, predominantly affecting

Figure 3. Axial CT chest shows near complete resolution of airspace disease in the lower lobes. There are bilateral residual trace pleural effusions.

the extremities³. However *M. abscessus* is more nosocomial and virulent and it causes disease in patients regardless of their immune status. Regarding antibiotic sensitivity, both *M. chelonae* and *M. abscessus* are resistant to most antibiotics, except to clarithromycin and amikacin³. *M. abscessus* is usually sensitive to ceftazidime whereas ceftazidime sensitivity of *M. chelonae* is variable³. Our patient was empirically started on ceftazidime based on this clinical observation. However, *M. abscessus* isolated from our patient was resistant to most antibiotics except tigecycline and amikacin. In fact the patient showed a rapid improvement of her symptoms and clinico-radiological findings after being started on tigecycline and amikacin. Subsequent sputum cultures were negative for *M. abscessus*.

Patients with localized *M. abscessus* infections respond well to appropriate treatment. The treatment approach to disseminated disease varies and is typically based on *in vitro* susceptibility testing. The goals of therapy should be more realistic and should include symptomatic improvements, radiographic regression of infiltrates, improvements in sputum culture positivity and conversion to negativity. A combination therapy of amikacin and ceftazidime or imipenem for 2 to 4 weeks is recommended, although the cost of therapy and morbidity has an effect on the treatment outcome. In cases of failure to treat with the above regimen or in cases of drug resistance, drugs showing efficacy *in vitro* against *M. abscessus*, such as linezolid, tigecycline (a tetracycline derivative) and telithromycin (a ketolide) have been shown to be effective⁴. *M. abscessus* isolated from our patient was resistant to most of the drugs and hence was treated with tigecycline. The patient presented a significant clinical, radiological improvement and also had a negative sputum conversion. Although *M. abscessus* species are rapid growers, the usual clinical course is indolent. To the best of our knowledge, no cases of rapid

progression of pulmonary disease to ARDS secondary to *M. abscessus* have been reported in the literature. Fulminant, rapidly progressive diseases with *M. abscessus* have been associated with gastroesophageal disorders and cystic fibrosis⁵. The diagnosis of *M. abscessus* is based on the diagnostic criteria formulated by the American Thoracic Society⁴. Although not considered as confirmatory tests, imaging studies and especially high resolution CT scans (HRCT) play an important role in the diagnosis and follow-up of *M. abscessus* infection. Non-tuberculous mycobacterial (NTM) infections are classified in two groups based on HRCT presenting either a cavitary pattern or a nodular bronchiectasis pattern with tree-in-bud appearance⁶. *M. abscessus* cases show widely scattered tree-in-bud appearance on CT chest⁷. Our patient presented the same characteristic appearance on her chest CT scan. Small centrilobular nodules of soft tissue attenuation interlinked to linear structures of similar size originating from a single stalk gives the characteristic tree-in-bud appearance on imaging studies⁸. Although this pattern was classically reported in mycobacterial infections, it has also been described in other infectious, inflammatory, immunologic and pulmonary vascular disorders⁹. Differential diagnosis of tree-in-bud appearance on CT scans in the setting of acute rapidly progressive disease should also include bacterial pneumonia, *Haemophilus influenza* infection, tumor emboli in the pulmonary vasculature and inhalation of toxic fumes⁹. Upon identifying this pattern on HRCT scans; work-up for the broad differentials should include a thorough medical history and clinical examination. The histopathological features contributing to this pattern in mycobacterial infection are the accumulation of caseous material within or around the bronchioles, with stalk and terminal tufts, a manifestation of caseous material in the terminal bronchioles and alveolar ducts, respectively⁸. The tree-in-bud sign is important in discriminating between phases of

unfavorable progression and phases of quiescence or resolution¹⁰. Chest CT scan is important when surgical intervention is planned or when assessing the effect of chemotherapy, as the resolution of the infection can be demonstrated sooner and quickly by radiological evidence.

In summary, our case report highlights the importance of identifying *M. abscessus* as a cause of severe respiratory failure requiring intense respiratory support and aggressive medical management. We also emphasize the importance of monitoring drug sensitivity in these cases as it would improve the chances of successful treatment of these potentially fatal infections.

Consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient's mother.

Author contributions

All authors have seen and approved the text of the manuscript and taken responsibility for its contents. Dr John has collected the relevant clinical data and drafted the article which was critically revised and edited by the co-authors, Dr Zangeneh and Dr Parthasarathy.

Competing interests

No competing interests were disclosed.

Grant information

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Michael Loebinger

National Institute for Health Research Respiratory Biomedical Research Unit, Royal Brompton & Harefield Hospital Foundation Trust and Imperial College London, London, UK

Steven Cowman

Imperial College London, London, UK

The authors describe a case of respiratory infection leading to ARDS which they suggest is secondary to *Mycobacterium abscessus* infection. They make this assumption based on the growth of *M. abscessus* from a tracheal aspirate in addition to the lack of improvement on meropenem, improvement on tigecycline and amikacin and the radiological findings.

This is an interesting case however the main issue is that the evidence that *M. abscessus* is the microbe responsible for the clinical course is unconvincing. A bacterial pneumonia followed by ARDS would be more likely in view of the previous history and timescale, and the radiology is non-specific as detailed by the previous reviewers. In addition the treatment regimen was short and non-standard for *M. abscessus* pulmonary infection and the response more rapid than would be expected.

It appears that *M. abscessus* was obtained from a single sputum (via tracheal aspirate) sample only which would be insufficient to meet diagnostic criteria for NTM infection. Repeated growths of this organism or a bronchoscopic sample would have been helpful in this case. A history of frequent respiratory tract infections is mentioned. It would be important to know if any samples had been sent for mycobacterial culture previously and in addition the number of subsequent samples post treatment.

In its present state we do not feel that the authors have convincingly demonstrated ARDS secondary to *M. abscessus* lung infection as per the title and would suggest that more evidence would be required before this case report is suitable for indexing.

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 27 June 2014

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Hartmut Lode

Department of Chest & Infectious Disease, Chest Hospital Heckeshom, Berlin, Germany

This case report on an ARDS probably induced by *M. abscessus* is an interesting clinical observation and broadens the etiologic spectrum of infections involved in ARDS.

The case is in general well described and the discussion addresses the current knowledge and problems with this pathogen. However, the first reviewer Dr. Griffith has already performed a critical review of this paper and has raised strong concerns for acceptance of the diagnosis of an infection by *M. abscessus*. Dr. Griffith is an outstanding expert in the field of nontuberculous mycobacterial infections and I do agree with most of the concerns raised by Dr. Griffith. However, the critical point of the case is whether *Pseudomonas* was the etiologic pathogen or not:

The authors are reporting that after one week of treatment with 3 times 500 mg meropenem daily, the patients' clinical findings worsen. - It would be helpful to know the body weight of the patient (sufficient meropenem doses?) and also some biomarkers of inflammation (start of therapy versus day 7), to have some additional objective data for the non-response. It would also be useful to include any data on the control of the trachea flora, concerning bacteria, on day 7.

Dr. Griffith has reservations in accepting the relatively fast response to the *M. abscessus* directed therapy, but even in more localized *M. abscessus* infections the median time until sputum conversion was only 1 month ([Jeon K et al.;AJRCCM 2009](#)).

In summary, the authors should give more information to demonstrate that *Pseudomonas* was not the etiologic pathogen as outlined above. The authors should also make a revision of the paper following all the proposals of Dr. Griffith.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 09 June 2014

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David E Griffith

Department of Medicine, University of Texas Health Sciences Center, Tyler, TX, USA

Comment #1: The authors correctly note that fulminant pneumonia due to *M. abscessus* to date has been limited to a very few clinical circumstances such as lipoid pneumonia and cystic fibrosis. To attribute fulminant pneumonia to *M. abscessus* in an entirely new setting requires rather rigorous "proof". For several reasons, I am not sure that "proof" exists for this case.

- a) The patient's course was consistent with bacterial pneumonia followed by adult respiratory distress syndrome.
- b) The patient had pseudomonas isolated from respiratory secretions and had multiple previous pneumonias presumably due to pseudomonas.
- c) Although tigecycline has less activity against pseudomonas than some other gram negative rods, it still has some activity and certainly amikacin has significant anti-pseudomonal activity.
- d) The radiographic findings were non-specific (as noted by the authors).
- e) The source of the *M. abscessus* in respiratory specimens could have been the tracheostomy site.
- f) The patient had rapid radiographic and microbiologic response, both unusual for *M. abscessus* lung disease with any antibiotic combination.
- g) The total length of treatment was very short for *M. abscessus* lung disease, and mostly with one agent.
- h) A biopsy would have been helpful for establishing the diagnosis.
- i) Is it possible the patient had ongoing aspiration (a factor that might account for some of the radiographic findings but might also support the mycobacterial diagnosis)?

Comment #2: I think the discussion is too ambitious. In my opinion the focus of the discussion should be persuading the reader about the veracity of the claim that *M. abscessus* caused this fulminate clinical course.

- a) The discussion about separating *M. chelonae* from *M. abscessus* in the lab is important, but can be summarized by the urgent need for widespread adoption of molecular methods not currently available in most mycobacteriology labs. There is no excuse *M. abscessus* to be

reported as part of a complex. To make things even more interesting, there appear to be 3 subspecies of *M. abscessus* (*abscessus*, *massiliense* and *boletti*). This problem is clearly peripheral to the thrust of the paper.

- b) The authors do not mention the major functional (and clinical) difference between *M. chelonae* and *M. abscessus* which is that *M. abscessus* has a functioning inducible macrolide resistance gene (*erm* gene) whereas *M. chelonae* does not. This means that *M. chelonae* isolates are usually macrolide susceptible while *M. abscessus* organisms are not. Again, this observation is somewhat peripheral to the main point of the manuscript.
- c) Overall, I think the discussion could be shortened with more focus on the main thrust of the manuscript

Comment #3: Some minor comments:

- a) The authors discuss treatment duration for *M. abscessus* infections as though the organism dictates the duration of therapy, rather duration of therapy is strongly dictated by the site of the infection. Duration of therapy differs between skin and soft tissue infection, lung disease, bone and joint disease, etc.
- b) In the case report, I would like to see the pCO₂ and HCO₃ levels and the anion gap.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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