Acute Respiratory Failure Involving an R Variant of *Mycobacterium abscessus*  

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We report the case of a cystic fibrosis patient colonized with a smooth-morphotype form of *Mycobacterium abscessus* who developed acute respiratory failure with the emergence of an isogenic rough (R) variant while he was recovering from peritonitis-induced shock. This report emphasizes the role of R forms in severe *M. abscessus* infections.  

**CASE REPORT**  

A 40-year-old man with cystic fibrosis (CF; ΔF508/W1282X genotype) diagnosed in 1993 was chronically colonized with *Staphylococcus aureus* and *Aspergillus fumigatus*, with negative *A. fumigatus* serology. *Mycobacterium abscessus* infection was diagnosed in early 1998. Antimycobacterial treatment was instituted between May 1999 and May 2001 and reinstituted between March 2002 and May 2003 (Fig. 1).  

In December 2003, the patient was admitted to the emergency unit of Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris, France, with a colic perforation and diffuse peritonitis secondary to a stercolith. Septic shock with severe hypoxemia occurred on day 1, requiring mechanical ventilation, inotropic adrenaline support, and treatment with combined antibiotics (ceftazidime, vancomycin, tobramycin, and ornidazole), hydrocortisone hemisuccinate, and drotrecogin alfa. Laboratory parameters showed lymphopenia (absolute lymphocyte count, 1,060/mm³) and raised serum transaminase levels (alanine aminotransferase level, 80 IU/liter, three times the upper limit of the normal range). The patient’s clinical status slowly improved. Bronchial aspiration performed on day 32 still yielded *A. fumigatus* and a rough (R) variant of *M. abscessus* (*M. abscessus* CF01-R). Positive *A. fumigatus* antigenemia results led to the initiation of antifungal therapy on day 9.  

Unexpectedly, septic shock recurred on day 11. Severe respiratory failure was present (ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen [PaO₂/FiO₂ index], 190), associated with patchy alveolar consolidation (Fig. 2). A surgical lung biopsy (right thoracotomy) was performed on day 12: the biopsy specimen culture was positive for an R-morphotype isolate of *M. abscessus* as the sole pathogen, with concordant histology showing a granulomatous epithelioid reaction with giant cells in areas of peribronchovascular fibrosis and multiple microabscesses. Antibiotic therapy was shifted empirically to imipenem-cilastin, amikacin, and clarithromycin on day 6. Nebulized amikacin was added to the systemic anti-M. *abscessus* therapy on day 56. The patient became apyrexial on day 77, and mechanical ventilation was stopped on day 83. The patient was discharged on day 128 (April 2004) under a regimen of clarithromycin monotherapy, which was maintained until April 2005. Sputum samples remained repeatedly positive for *M. abscessus* (R form) throughout treatment (Fig. 1). At the last examination, on December 2006, the patient had Medical Research Council class II dyspnea and a good general status, without any clinical or radiological manifestation of mycobacterial lung disease.  

Six representative *M. abscessus* isolates (one smooth [S] variant and five R variants) recovered between April 1999 and December 2006 were studied. *hsp65* (17) and *rpoB* (1) sequence-based identification yielded *M. abscessus* sensu stricto for all six isolates. Randomly amplified polymorphic DNA PCR analysis (24) and multilocus sequence typing (data not shown) confirmed the clonal nature of the isolates of different morphotypes (Fig. 3). These results established the persistence of a single clone of *M. abscessus* for a period of 8 years, despite several courses of aggressive antibiotic...
therapy, in agreement with the data in a previous report by Cullen et al. (5) but involving an S-to-R switch.

*P. abscessus* is a rapidly growing mycobacterium now recognized as the main nontuberculous mycobacterium pathogen in CF (6, 9, 15, 16, 20). According to previous reports, the range in the clinical expression of *P. abscessus* lung infections extends from apparently asymptomatic infection to severe, life-threatening disease (5, 7, 8, 19, 23). *P. abscessus* may grow on solid medium, with S and R morphotypes recognized by the appearances of the colonies (2, 10). The role of S-R variation in the pathogenesis of *P. abscessus* is unclear, but R forms have increased virulence in murine models compared to S forms (2, 3, 10, 11, 18). The data in this report and other recent

![FIG. 1. Dynamics of pulmonary function, microbiological results, and antimycobacterial treatments (identified as 1st, 2nd, and 3rd).](image)

*a*, Regimen of clarithromycin, ciprofloxacin, and doxycycline; *b*, regimen of clarithromycin, imipenem (5 months), amikacin (4½ months), and nebulized amikacin (6 months). Open and closed circles represent negative and positive culture results, respectively; letters above the circles indicate the samples studied (where no sample is listed, sputum samples were used), and letters below indicate the *P. abscessus* morphotypes (where no morphotype is given, the morphotype was not determined). Abbreviations: PB, pulmonary biopsy specimen; BAL, bronchoalveolar lavage fluid; and FEV, forced expiratory volume.

![FIG. 2. Patient's chest radiographs at admission (A) and at day 12 (B).](image)
studies strongly suggest that the most severe forms of lung infection may be linked to the involvement of R variants of the bacterium (12). Further prospective studies should clarify this point.

S variants of \textit{M. abscessus}—probably the principal form living in the environment—are found at early stages of infections, whereas R variants generally appear several years later, gradually and completely replacing the S variants initially present (12). Clinical diseases due to R variants often emerge in CF patients following the weakening of immune defenses due to transplantation and immunosuppressive treatment (4, 19, 22) or septic shock, as in the case reported here. \textit{Aspergillus} infection is a statistically significant predictor for nontuberculous mycobacterium infection (13) and may also have created favorable conditions for the development of the M. \textit{abscessus} R variant in our patient. R variants, which appear spontaneously at very low frequencies in vitro (range of 1 R variant in 10^6 to 1 R variant in 10^8 S cells) (11), thus seem to be selected in vivo, probably through interactions between the host and the bacterium involving the immune system (18). Systemic steroids and nonsteroidal anti-inflammatory drugs may trigger this process, as they have been associated previously with the occurrence of severe M. \textit{abscessus} infections (4, 14). Our patient had lymphopenia and high transaminase levels, two factors recently shown to be predictive of acute respiratory distress syndrome in tuberculosis patients (21). These factors may also predispose patients infected with R variants of \textit{M. abscessus} to acute respiratory failure.

This case report shows that it is important to differentiate between S and R variants of \textit{M. abscessus}. These morphotypes can be differentiated on the basis of the appearance of colonies on commonly used solid medium. The isolation of R variants should lead to greater prudence in the situations favoring their development (e.g., transplantation and immunosuppressive therapy). Work is needed to identify the factors associated with the S-to-R switch of \textit{M. abscessus} in the lungs and determine whether lung infections with these variants require a particular type of therapeutic management (e.g., more aggressive therapeutic measures and the avoidance of lung transplantation).

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REFERENCES


FIG. 3. Randomly amplified polymorphic DNA PCR patterns of our patient’s six \textit{M. abscessus} isolates with the primer OPA2 (lane 1, S morphotype, and lanes 2 to 6, R morphotypes) compared to those of the type strain \textit{M. abscessus} ATCC 19977 (R and S phenotypes) (lanes 7 and 8).


