A Case of Pulmonary *Mycobacterium abscessus* Subspecies *abscessus* Disease That Showed a Discrepancy Between the Genotype and Phenotype of Clarithromycin Resistance

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**Abstract:**
*Mycobacterium abscessus* subspecies *abscessus* is major subspecies in the *M. abscessus* complex and is usually refractory to standard antibiotherapy. Genetic tracing of *erm*(41) T28 is a mechanism for monitoring macrolide resistance. We treated a patient with a pulmonary infection caused by *M. abscessus* subsp. *abscessus* with the *erm*(41) T28 polymorphism, which was susceptible to clarithromycin, and his clinical treatment course was good. The identification of the *M. abscessus* complex genotype is important, but clinical confirmation of clarithromycin susceptibility is also needed to plan individual treatment strategies.

**Key words:** *Mycobacterium abscessus*, inducible resistance, *erm*(41)


**Introduction**

The prevalence of non-tuberculous mycobacteria (NTM) infection has been increasing worldwide (1-3). *Mycobacterium abscessus* complex belongs to a member of the rapidly growing mycobacteria (RGM) group among NTM, and the frequency of RGM differs among regions; for example, it is 3% in Japan (4) and 5% in Australia (5). However, in Korea, the frequency is 33%, which is the second highest frequency after that of *Mycobacterium avium* complex (MAC) (6).

From a clinical aspect, the importance of this species is that it is often refractory to antibacterial treatment. In recent years, *M. abscessus* complex has been classified into *M. abscessus* subsp. *abscessus* (*M. abscessus*), *M. abscessus* subsp. *massiliense* (*M. massiliense*), and *M. abscessus* subsp. *bolletii* (*M. bolletii*) (7, 8). The *Mycobacterium abscessus* complex has acquired resistance by point mutations in the *rrl* gene at positions 2,057-2,059 (9, 10). In addition, *M. abscessus* and *M. bolletii* have inducible resistance to macrolide, which is induced by *erm*(41), whereas *M. massiliense* has a dysfunctional *erm*(41) due to two characteristic deletions and is susceptible to macrolides (11, 12). The response rate to antibiotic therapy including clarithromycin (CAM) was much higher in patients with pulmonary *M. massiliense* disease than in those with pulmonary *M. abscessus* disease due to the function of *erm*(41). Furthermore, *M. abscessus* strains harbor a T/C polymorphism at the 28th nucleotide in *erm*(41). T28 sequvar strains (Trp10 codon) demonstrate inducible CAM resistance, while C28 strains (Arg10 codon) are susceptible to CAM (13). Therefore, identification of *M. abscessus* complex subspecies and genetic typing of *erm*(41) have clinical value for predicting the efficacy of antibiotic therapy and developing appropriate treatment strategies.

We herein report the case of a 55-year-old man with pulmonary *M. abscessus* infection whose clinical course differed from that predicted based on subspecies identification and *erm*(41) typing.

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We herein present a case of pulmonary *M. abscessus* disease caused by *M. abscessus* carrying *erm(41)* T28 sequevar. Although this genotype tends to suggest resistance to CAM (13), the strain was susceptible to CAM without inducible resistance and the patient showed a good clinical response to CAM-containing antimicrobial treatment. Therefore, the genotype of *erm(41)* T28 sequevar in pulmonary *M. abscessus* disease did not predict a poor clinical response in this case.

Recently, Yoshida et al. reported that a subset of *M. abscessus* isolates (9.5%) presented with genetically functional *erm(41)* but no phenotypic inducible resistance (15), as observed in the strain isolated from our patient. Previous reports that investigated the *erm(41)* sequevar classification may have failed to predict inducible resistance correctly (15, 16). These findings suggest the importance of carrying out DST for CAM during the development of treatment strategies for *M. abscessus* infection without relying solely on identification using a genetic approach.

The Clinical and Laboratory Standards Institute recommends that DST be performed with culturing at 30°C and determined 3 days later using cation-adjusted Mueller-Hinton broth (pH 7.4) for RGM (17). If the strain is resistant on day 3, then resistance is caused by the *rrl* gene mutation. If the strain is judged to be sensitive to CAM on day 3, assessing the inducible resistance, which is associated with the *erm(41)* gene (18, 19), should be carried out using an additional extended culture with an assessment on day 14. In Japanese clinical practice, DST of NTM is usually performed using a BrothMIC NTM® kit with Middlebrook 7.
H9 (Kyokuto Pharmaceutical Industrial Co., Ltd., Tokyo, Japan) as the liquid growth medium and culturing at 37°C. However, a BrothMIC NTM® kit is inadequate for RGM. We attempted DST using BrothMIC NTM® and obtained a different result at the late phase on day 14 compared to our findings using the recommended method (Table). In addition, sequencing of the \( \text{erm}(41) \) gene is a particularly important diagnostic tool for assessing the clarithromycin susceptibility in isolates of \( M. \text{abscessus} \) complex, although, genetic identification for \( M. \text{abscessus} \) complex is not performed in clinical Mycobacterium laboratories in Japan. The development of kits that can be used for RGM is therefore needed.

In the present case, \( M. \text{abscessus} \) infection was detected by the onset of pneumothorax. The frequency of pneumothorax complications is reported to be 4.1% in pulmonary NTM disease (20). Regarding the \( M. \text{abscessus} \) complex, some cases with complication of pneumothorax have been reported (21-23). In the present case, lung image findings revealed consolidation with cavities near the pleura, which is a possible cause of pneumothorax. If \( M. \text{abscessus} \) complex infection is misdiagnosed as MAC, inadequate treatment can result in a poor treatment course. Physicians should therefore consider \( M. \text{abscessus} \) complex as a causative disease of pneumothorax.
In conclusion, we encountered a case of pulmonary *M. abscessus* infection in which the isolated strain showed discrepancies between the genotype and phenotype concerning CAM resistance. Identifying the *M. abscessus* complex species and the *erm* (41) genotype is crucial; however, carrying out DST for CAM also has importance in properly treating this infection.

The authors state that they have no Conflict of Interest (COI).

**References**

22. Pang YK, Ngeow YF, Wong YL, Llam CK. Mycobacterium abscessus - to treat or not to treat. Respirol case reports **1**: 31-33, 2013.