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Case Report

# The first case of pulmonary disease caused by *Mycobacterium septicum* in China

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SUMMARY

*Mycobacterium septicum* is a rapidly growing Mycobacterium (RGM) that rarely causes pulmonary disease globally. We describe a case of *M. septicum* pulmonary disease, which to our knowledge is the first reported in China. The isolates were identified as *M. septicum* and were susceptible in vitro to amikacin, ciprofloxacin, ofloxacin, levofloxacin, kanamycin, and sulfamethoxazole.



## 1. Introduction

*Mycobacterium septicum* is a rapidly growing non-tuberculous Mycobacterium (NTM), and has been identified phenotypically as a member of the *Mycobacterium fortuitum* third biovariant complex.[1,2] There are a few reports of *M. septicum* infections, but cases of pulmonary disease caused by *M. septicum* are rare. To our knowledge, no other case of *M. septicum* infection has been reported in China thus far. We report herein a case of *M. septicum* infection in a patient suffering from pulmonary disease.

## 2. Case report

A 42-year-old man was admitted to the local hospital with a 3-month history of cough and weight loss of 10 kg on August 17, 2010. Before admission, the patient had visited the local clinic and had been treated with anti-inflammatories and cough medicine; however his condition failed to improve.

A chest computed tomography image showed fibrous cavernous shadows of irregular size and shape in the lung apex bilaterally and in the inferior lingular segment of the left lung. The largest shadow was 6.1 cm × 4.5 cm; multiple nodule shadows with diameters of about 0.2–0.5 cm were irregularly distributed throughout the lungs bilaterally. Their boundaries were obscure, while lung markings were found to be increased and thickened along with lymph node shadows in the mediastinum. The diagnostic impression was chronic fibro-cavitary pulmonary tuberculosis with bilateral lung dissemination. On August 18, 2010, the patient was referred to the local institute for tuberculosis control and prevention. On August 18 and 20, 2010, bacteriological examinations showed that a sputum smear and culture test were positive for acid-fast bacilli (AFB). He was diagnosed in the local institute with chronic fibro-cavitary pulmonary tuberculosis with bilateral lung hematogenous dissemination II. In August 2010, a 2-month intensive phase and a 4-month continuous phase (2H3R3Z3E3/4H3R3. H: isoniazid, R: rifampicin, Z: pyrazinamide, E: ethambutol) were initiated as therapeutic regimens under full-course supervision and management, adding levofloxacin for 1 month. On October 12, 2010 and January 13 and February 14, 2011, sputum smears for AFB were negative. The patient's condition improved and the treatments were stopped on February 16, 2011. Unfortunately he relapsed in March 2012, and sputum smear and cultures again tested positive for AFB. The strain, numbered SC11091, was stored and identified at the National Tuberculosis Reference Laboratory (NTRL), National Institute for Communicable Disease Control and Prevention (ICDC), Chinese Center for Disease Control and Prevention (China CDC).

Antimicrobial susceptibility tests[3,4] were performed using a microplate Alamar blue assay (AbD Serotec, USA) (MBA)[5,6] and Etest (bioMérieux, Solna, Sweden).[4] The control group was *M. septicum* reference strain DSM 44393. Table 1 shows that SC11091, similar to the reference strain, was resistant to most

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**Table 1**
Minimum inhibitory concentrations (MICs) of drug sensitivity test on *Mycobacterium septicum* DSMZ 44393 and SC11091

| No. | Drugs | Intermediate | | *M. septicum* DSMZ 44393 | | SC11091 | |
|---|---|---|---|---|---|---|---|
| | | Etest[8] | MBA[1,6,7] | Etest | MBA | Etest | MBA |
| 1 | Rifampin | 1–4 | 0.1 | ≥32 (+) | 64 (+) | ≥32 (+) | 64 (+) |
| 2 | Isoniazid | [a] | 1 | [a] | >256 (+) | [a] | >256 (+) |
| 3 | Streptomycin | 1 | 5 | 16 (−) | 16 (+) | 32 (−) | 32 (+) |
| 4 | Ethambutol | 0.064–0.25 | 1 | 0.75 (+) | 8 (+) | 6 (+) | >256 (+) |
| 5 | Amikacin | 16–64 | 16–64 | 0.38 (−) | 0.5 (−) | 0.5 (−) | 4 (−) |
| 6 | Ciprofloxacin | 16–128 | 1–4 | 0.023 (−) | 0.25 (−) | 0.032 (−) | 0.25 (−) |
| 7 | Ofloxacin | 2–8 | 2–8 | 0.125 (−) | 0.5 (−) | 0.094 (−) | 0.5 (−) |
| 8 | Kanamycin | 16–64 | 16–64 | 1.5 (−) | 4 (−) | 3 (−) | 4 (−) |
| 9 | Ethionamide | 0.016–0.064 | 0.016–0.064 | ≥256 (+) | >256 (+) | ≥256 (+) | >256 (+) |
| 10 | Linezolid | 8–32 | 8–32 | 1.0 (−) | 2 (−) | 8 (−) | 8 (−) |
| 11 | Azithromycin | 2–8 | [a] | ≥6 (−) | [a] | 48 (+) | [a] |
| 12 | Clarithromycin | 2–8 | [a] | 3 (−) | [a] | ≥256 (+) | [a] |
| 13 | Imipenem | 4–16 | [a] | 1 (−) | [a] | 3 (−) | [a] |
| 14 | Quinupristin | 1–4 | [a] | ≥32 (+) | [a] | ≥32 (+) | [a] |
| 15 | Tigecycline | 1–2 | [a] | 0.064 (−) | [a] | 0.064 (−) | [a] |
| 16 | Capreomycin | [a] | [b] | [a] | 2 | [a] | 2 |
| 17 | *p*-Aminosalicylic acid | [a] | [b] | [a] | >256 | [a] | >256 |
| 18 | Dipasic | [a] | [b] | [a] | >256 | [a] | >256 |
| 19 | Tetracycline | [a] | [b] | [a] | 8 | [a] | >128 |
| 20 | Doxycycline | [a] | 16 | [a] | 16 (+) | [a] | >256 (+) |
| 21 | Sulfamethoxazole | [a] | 32 | [a] | >256 (+) | [a] | 16 (−) |
| 22 | Minocycline | [a] | 16 | [a] | 8 (−) | [a] | >256 (+) |
| 23 | Cefoxitin | [a] | 16–128 | [a] | 16 (+) | [a] | >256 (+) |
| 24 | Levofloxacin | [a] | 2–8 | [a] | 0.25 (−) | [a] | 0.125 (−) |

MBA, microplate Alamar blue assay; (+), resistant; (−), susceptible.
[a] No intermediate was available.
[b] No test under the item.

anti-tuberculosis drugs including the first-line drugs isoniazid, rifampin, streptomycin, and ethambutol; however it was susceptible in vitro to amikacin, ciprofloxacin, ofloxacin, levofloxacin, kanamycin, and sulfamethoxazole.

The isolates that were positive for AFB were proven to be NTM using the improved Lowenstein–Jensen medium, *para*-nitrobenzoic acid (PNB) and thiophene-2-hydrazine carboxylic acid (TCH) media, and multilocus PCR.[7] The sequences of the gene *hsp*65[8,9]/*rpo*B[10] were sent to the BLAST online database for sequence alignment and were found to be similar to *M. septicum* strain ATCC 700731, achieving a 99% match. Using MEGA version 5.01 software package, the phylogenetic consensus tree based on *hsp*65 sequences illustrated the position of the strain SC11091, which was nearest to *M. septicum* strain ATCC 700731 and DSM 44393 (Figure 1).

## 3. Discussion

The patient was admitted to the local hospital with a persistent cough, and sputum samples were isolated and found to be

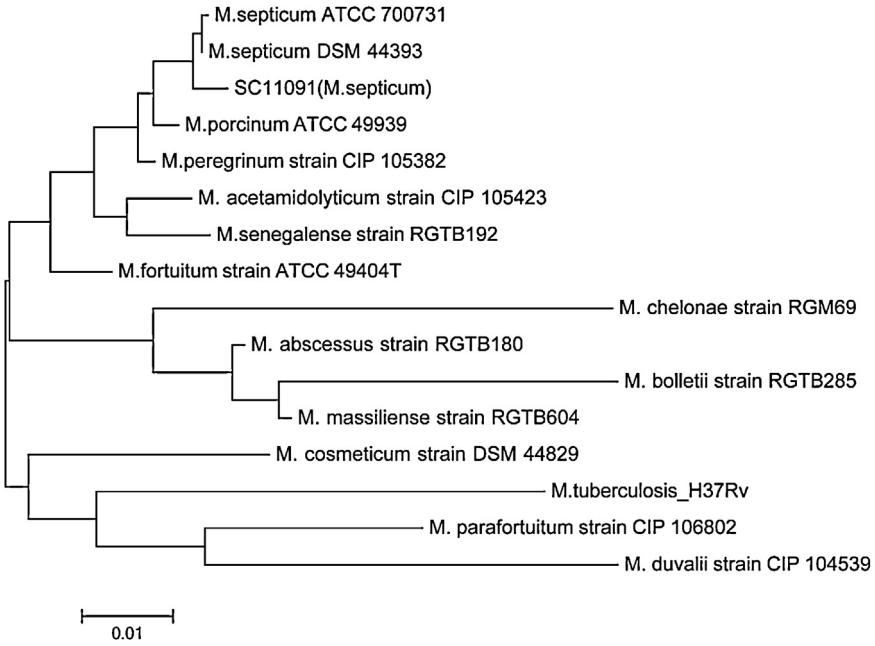


**Figure 1.** The phylogenetic consensus tree based on *hsp*65 sequences illustrating the position of SC11091 and some reference strains of Mycobacterium. The tree was rooted using *Mycobacterium tuberculosis* H37Rv as the out-group. Scale bar, 1% difference in the sequences.

AFB-positive on culture. Combining clinical and bacteriologic examinations with molecular biological identification results, the patient was finally diagnosed with pulmonary disease caused by *M. septicum*, as the clinical manifestations were similar to those of pulmonary diseases caused by *M. tuberculosis*. As usual, it was difficult to distinguish pulmonary disease caused by NTM from that caused by *M. tuberculosis*, because they have the same symptoms and AFB results. This confusion often leads to misdiagnosis, resulting in a series of mistakes, e.g., inadequate treatment regime, delayed healing of diseases, relapses, and the generation of multidrug-resistant (MDR) or extensively drug-resistant (XDR) mycobacteria.

Though the patient improved after using the therapeutic regimens 2H3R3Z3E3/4H3R3 under full-course supervision and management and the addition of levofloxacin for 1 month, he relapsed within 1 year of stopping the treatment. Sputum smear and culture tests were also positive for AFB. There are several reasons for a discussion of this case. First, in China, although patients with tuberculosis receive treatment either at the local tuberculosis institute or at hospitals, it might not be effective for them. Second, there is no effective treatment program for NTM diseases in the world, because most NTM, as opportunistic pathogens, display multidrug resistance to anti-tuberculosis drugs in nature. Third, minimum inhibitory concentrations (MICs) for the isolate showed that the pathogen was susceptible to levofloxacin; however this modification led to treatment failure or relapse.[11] Also, the American Thoracic Society (ATS) has stated that susceptibility testing of clinically significant rapidly growing mycobacteria (RGM; e.g., *M. fortuitum*, *M. abscessus*, and *M. chelonae*) should not be performed with anti-tuberculosis agents.[12] Therefore, further investigations are necessary.

Since 2000, *M. septicum* has been identified, named,[2] and described as the cause of various human infections. There have been several reports of *M. septicum* infection in other parts of the body, while pulmonary disease has rarely been reported worldwide. *M. septicum* is an opportunistic pathogen, similar to many other NTM species. In 2000, the organism was reported to be one species of the *M. fortuitum* complex, and known as the unnamed third biovariant complex.[13] Species belonging to the *M. fortuitum* group are a relatively rare cause of disseminated mycobacterial pulmonary disease.[11] Further, most of the isolates that have been studied have been environmental strains and none have had a definite disease association.[11] Here, we have described a case of pulmonary disease caused by *M. septicum*, which is the first report in China. The isolates were identified using both conventional microbiological methods and *hsp*65 and *rpo*B gene sequence analysis. Further, the phylogenetic consensus tree based on *hsp*65 sequences shows that the sequence of SC11091 is closer to that of *M. septicum* strain ATCC 700731 and DSM 44393.

Our findings show that *M. septicum*, despite being rare, is capable of causing pulmonary disease. Furthermore, in the clinical and laboratory diagnosis of rare NTM infectious disease, NTM species should be isolated and identified in order to avoid delays in the diagnosis and treatment and to prevent failure or relapse.

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