



## Case Report

Pulmonary *Mycobacterium heckeshornense* infection in a healthy womanFumio Kurosaki<sup>a,\*</sup>, Taichiro Yoshimoto<sup>b</sup>, Masayuki Nakayama<sup>a</sup>, Masashi Bando<sup>a</sup>, Koichi Hagiwara<sup>a</sup><sup>a</sup> Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan<sup>b</sup> Division of Integrative Pathology, Jichi Medical University, Shimotsuke, Tochigi, Japan

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## ABSTRACT

Pulmonary infection due to *Mycobacterium heckeshornense* (*M. heckeshornense*) in healthy adults without underlying diseases is very rare and optimal treatments have not yet been established. A 39-year-old woman was admitted to our hospital for further examinations following the identification of a pulmonary cavitary nodule. Acid-fast bacilli were cultured from specimens obtained by bronchofiberscopy, and identified with *M. heckeshornense* using nucleotide sequencing. Antimycobacterial chemotherapy was effective temporarily, while the nodular lesion subsequently worsened. The patient underwent lobectomy and has not relapsed thus far. A lung specimen showed marked granulomatous inflammation with extensive caseous necrosis and the preservation of some parts of alveolar septa within caseous necrosis, indicating an exudative process and resistance to chemotherapy. *M. heckeshornense* is strongly pathogenic and switching to surgical intervention needs to be considered when chemotherapy is insufficient.

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## 1. Introduction

With the development of bacterial analyses such as DNA sequencing analyses, more than 150 species of non-tuberculous mycobacteria (NTM) have been identified [1]. *Mycobacterium heckeshornense* (*M. heckeshornense*) is a pathogenic and slow-growing NTM that was first described in 2000 [2]. A limited number of cases of this infection have been reported to date [2–14], with most being pulmonary infections in immunocompetent patients presenting with underlying lung diseases [2–8]. Optimal treatments for *M. heckeshornense* infection have not yet been established, and antimycobacterial therapy or the removal of an infective nidus have been attempted. We herein report a case of pulmonary infection due to *M. heckeshornense* in a healthy woman, who was successfully treated by antimycobacterial therapy and subsequent surgical intervention. This report will be helpful for clinicians treating *M. heckeshornense*.

## 2. Case report

A formerly healthy 39-year-old Japanese woman was admitted to our hospital for further examinations following an abnormal chest radiograph in 2012. She had no specific thoracic symptoms. She was a teacher and had been working in Madagascar for two years four years before admission. She has never smoked and has never been pregnant.

A physical examination upon admission revealed that she was afebrile and her vital signs were stable. The lymph nodes were not palpable, and the results of a physical examination were normal: blood pressure, 95/58 mmHg; pulse, 65 beats/min; temperature, 36.9 °C; height, 159 cm; weight, 55 kg; body mass index, 21.8 kg/m<sup>2</sup>. Chemical and hematological laboratory tests were unremarkable: white blood cell count,  $4.9 \times 10^3/\mu\text{L}$ ; hemoglobin, 12.3 g/dL; platelet count,  $17.5 \times 10^4/\mu\text{L}$ ; C-reactive protein, 0.02 mg/dL. Serum 1, 3- $\beta$ -D glucan, the *Aspergillus galactomannan* antigen, cryptococcal antigen, hepatitis B surface antigen, hepatitis C virus antibody, rapid plasma regain test, *Treponema pallidum* hemagglutination test, and human immunodeficiency virus (HIV) antibody were all negative. No significant bacteria or fungi were detected in the patient's blood or sputum cultures, and a QuantiFERON TB-3G test yielded a negative result. A chest

\* Corresponding author. Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan.

E-mail address: [fumio-kuro@jichi.ac.jp](mailto:fumio-kuro@jichi.ac.jp) (F. Kurosaki).

radiograph and chest computed tomography (CT) scan performed on admission revealed a solitary pulmonary nodule with a thick-walled cavity and an infiltrative shadow surrounding a nodule in the right upper lung, and did not show underlying lung diseases (Fig. 1). In addition, abnormal shadows were not recognized in a health examination conducted one year previously. Trans-bronchial lung biopsy (TBLB) was performed, and showed epithelioid granulomas with caseous necrosis and multinucleated giant cells (Fig. 2a). Many acid-fast bacilli were detected within necrotic areas by Ziehl-Neelsen staining (Fig. 2b), and polymerase chain reaction (PCR) tests for *Mycobacterium tuberculosis* (COBAS Taqman MTB; Roche Diagnostics, Tokyo, Japan) and *Mycobacterium avium complex* (COBAS Taqman MAI; Roche Diagnostics) were negative.

At this point, we were unable to exclude tuberculosis based on pathological findings and her recent stay in Africa. Therefore, we initially administered the patient four drug treatments including isoniazid (INH) 300 mg/day, rifampicin (RFP) 450 mg/day, ethambutol (EB) 750 mg/day, and pyrazinamide (PZA) 1.2 g/day. A biopsy sample and bronchial washing fluid culture for mycobacterium formed only a few colonies in 2% Ogawa egg slant medium (Kyokuto, Tokyo, Japan) after two months, and there were no matches with any of the 18 mycobacterial species in DNA-DNA hybridization (DDH Mycobacteria; Kyokuto). In order to identify this isolate, nucleotide sequencing was performed targeting fragments of the 16S ribosomal RNA (16S rRNA), RNA polymerase B (*rpoB*), and heat shock protein 65 (*hsp65*) genes. The results of the sequence analysis were consistent with *M. heckeshornense* (100% in 16S rRNA, 100% in *rpoB*, and 100% in *hsp65*), and, thus, this strain was identified as *M. heckeshornense*. This strain was subsequently proven to grow at 42 °C, but did not grow well at 37 °C. The results of antimicrobial susceptibility tests (BrothMIC NTM; Kyokuto) showed susceptibility to RFP (Minimum Inhibitory Concentration [MIC], 0.06 µg/mL), EB (MIC, 0.5 µg/mL), and clarithromycin (CAM) (MIC, 0.06 µg/mL). We then changed her treatment to RFP 450 mg/day, EB 750 mg/day, and CAM 800 mg/day following the identification of *M. heckeshornense*.

Although her radiographic findings transiently improved, the nodule with a cavity and surrounding infiltrative shadow gradually worsened, which indicated that the strain had become resistant to the antimicrobials. Therefore, she underwent right upper

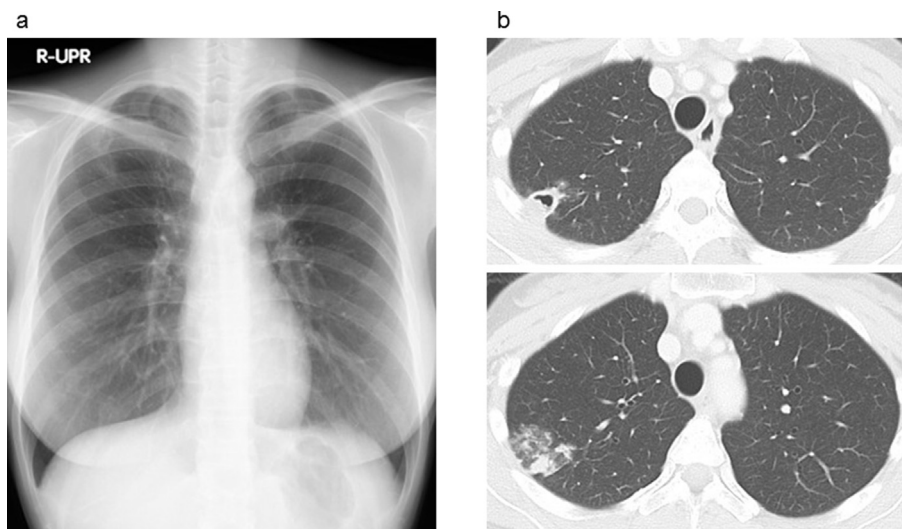
lobectomy by video-assisted thoracoscopic surgery (VATS) two years after the first admission (in 2014). A lung gross specimen revealed a cavity (2.0 × 1.6 cm in size) with extensive caseous necrosis (Fig. 3a). Histopathological findings showed marked granulomatous inflammation with some Langhans giant cells around caseous necrosis and acid-fast bacilli around the cavity wall (Fig. 3b). These findings also revealed that some parts of alveolar septa were preserved within caseous necrosis (Fig. 3c). Excised tissue was not cultured due to formalin fixation. She completed a 12-month course of antimycobacterial therapy (RFP, EB, and CAM) after lobectomy, and has not relapsed during the follow-up. Her sputum culture has been negative for mycobacterium throughout the clinical course. The clinical course to date is shown in Fig. 4.

### 3. Discussion

This case provided two clinical suggestions. A healthy adult without underlying lung diseases may develop pulmonary infection by *M. heckeshornense*. Furthermore, removal of an infective nidus by VATS is effective as a radical cure.

*M. heckeshornense* was first reported in 2000 as a slow growing scotochromogenic NTM [2] and resembles *M. xenopi* phenotypically and phylogenetically [2,7]. However, drug susceptibility was found to differ [4,6,7,12,13]; *M. heckeshornense* typically shows susceptibility to EB, whereas *M. xenopi* does not. Therefore, it is important to distinguish between them precisely in order to select effective drugs. *M. heckeshornense* is not identified or has often been misidentified as *M. xenopi* by the DDH method due to genomic similarities [4,6,7]. The DDH method may not have the ability to distinguish species that are closely related genomically because it provides an assessment of overall similarities in heritable material, with phylogenetic data providing information on neighboring organisms [15,16]. On the other hand, nucleotide sequencing is easily conducted and provides accurate information from sequence analyses on the 16S rRNA, *rpoB*, and *hsp65* genes [4,7,17].

To the best of our knowledge, there have been 15 cases of human infection with *M. heckeshornense*, excluding our case [2–14], 9 of which pulmonary infectious cases [2–8]. Most pulmonary infectious cases were reported in immunocompetent patients with underlying lung diseases such as emphysema [6], old pulmonary tuberculosis [4], pneumoconiosis [4], and lung scarring from



**Fig. 1.** (a) A chest radiograph in 2012 showing a pulmonary nodule with a cavity and an infiltrative shadow surrounding a nodule in the right upper lung field. (b) A chest CT scan in 2012 showing a pulmonary nodule (1.7 × 1.4 cm in size) with a thick-walled cavity, and an infiltrative shadow surrounding a nodule in the right S<sup>1</sup> area. It does not show underlying lung diseases.

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