CASE REPORT

A case of pulmonary *Mycobacterium heckeshornense* infection coexisted with lung cancer

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Abstract : A 71-year-old male was referred to our institution for further examination of chest abnormal shadow. A cavitation in the right apical region, a mass adjacent to the pleura in the right upper lobe, and a nodule in the right middle lobe were observed in a chest computed tomography. The sputum smear and culture of acid-fast bacilli were positive, and *Mycobacterium heckeshornense* (*M. heckeshornense*) was identified with the matrix-assisted laser desorption ionization time-of-flight mass spectroscopy. Moreover, computed tomography-guided biopsy of a mass adjacent to the pleura in the right upper lobe yielded the diagnosis of primary lung adenocarcinoma. Taken together, the patient was finally diagnosed as coexistence of pulmonary *M. heckeshornense* infection and primary lung cancer. An anti-mycobacterial treatment with rifampicin, ethambutol and clarithromycin and a combined chemotherapy were fairly successful for pulmonary *M. heckeshornense* infection and primary lung adenocarcinoma, respectively. These observations suggest that triple anti-mycobacterial therapy may contribute to good controls of *M. heckeshornense* infection and that careful selection of anti-cancer drugs against lung cancer might be lead to favorable outcomes even during the course of anti-mycobacterial treatment. To the best of our knowledge, this is the first report of pulmonary *M. heckeshornense* infection coexisted with lung cancer. J. Med. Invest. 71 : 327-331, August, 2024

Keywords **:** *Mycobacterium heckeshornense, non-tuberculous mycobacterium, lung cancer*

INTRODUCTION

Mycobacterium (*M.*) *heckeshornense* is a quite rare non-tuberculous mycobacterium (NTM) that was named after the clinic where it was first treated (the Heckeshorn Lung Clinic). *M. heckeshornense* was first identified in a patient with severe cavitary pulmonary disease in 2000 (1), and has been reported to cause infection in multiple sites, including tenosynovitis (2), lumbar spondylodiscitis (3), lymphadenitis (4) and peritonitis (5) besides pulmonary infectious diseases. The pathogenesis of *M. heckeshornense* remains to be elucidated, although the species have been demonstrated to infect both immunocompromised and immunocompetent patients (1, 3, 5, 6).

Preexisting pulmonary diseases, especially chronic obstructive pulmonary disease (COPD), interstitial lung diseases, bronchiectasis and pulmonary tuberculosis make patients susceptible to non-tuberculous mycobacterium lung disease (NTM-LD) (7, 8). Previous studies have also demonstrated a relationship between NTM-LD and lung cancer. In these studies, NTM-LD was associated with lung cancer in 2.0-7.3% of cases (7, 9). The common pathogens of NTM-LD coexisted with lung cancer were shown to be *M. avium* (31.0%) and *M. intracellulare* (31.0%) followed by *M. kansasii* (13.8%) and *M. gordonae* (13.8%) (10), however, coincidence of *M. heckeshornense* and lung cancer has never been reported before.

We herein report a case of pulmonary *M. heckeshornense* infection coexisted with primary lung adenocarcinoma. Triple anti-mycobacterial therapy with rifampicin (RFP), ethambutol (EB) and clarithromycin (CAM), and a combined chemotherapy with carboplatin (CBDCA), pemetrexed (PEM) and pembrolizumab were fairly successful for the treatment of *M. heckeshornense* infection and lung adenocarcinoma, respectively. To the best of our knowledge, this is the first report of pulmonary *M. heckeshornense* infection coexisted with lung cancer.

CASE PRESENTATION

A 71-year-old male with hemosputum was referred to our institution for further examination of abnormal shadows on a chest X-ray in a medical checkup. He had medical histories of gastric ulcer and pneumonia, and had comorbidities of COPD, hypertension and type 2 diabetes mellitus. He was a current smoker with smoking index of 78 pack-years. Physical findings at

Abbreviations :
M., Mycobacterium ; NTM, non-tuberculous mycobacterium ; COPD, chronic obstructive pulmonary disease ; NTM-LD, non-tuberculous mycobacterium lung disease ; RFP, rifampicin ; EB, ethambutol ; CAM, clarithromycin ; CBDCA, carboplatin ; PEM, pemetrexed ; MAC, *Mycobacterium avium* complex ; CT, computed tomography ; PET, positron emission tomography ; SUVmax, maximum standardized uptake value ; AFB, acid-fast bacilli ; MGIT, mycobacterium growth indicator tube ; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectroscopy

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the initial admission revealed a height of 168 cm, a weight of 56 kg, an Eastern Cooperative Oncology Group performance status of 1, a body temperature of 36.4℃, a blood pressure of 165/72 mmHg, and a pulse of 94 beats per minute and a percutaneous oxygen saturation of 97% on room air. A cardiovascular examination was unremarkable. On chest auscultation, breath sounds were normal. The laboratory data showed mild neutrophilia and elevated erythrocyte sedimentation rate. The serum level of carcinoembryonic antigen was mildly elevated. T-SPOT.TB test was positive, while anti-*M. avium* complex (MAC) antibody, *Aspergillus* galactomannan antigen and β-D-glucan were negative. The remainder of laboratory test results is shown in Table 1. A chest X-ray revealed a cavitation with pleural thickening and a mass in the right upper lung field (Fig. 1A). A chest computed tomography (CT) scan showed a cavity with a thick wall in the right apical region, a mass adjacent to the pleura in the right upper lobe, and a nodule in the right middle lobe. No enlarged lymph nodes in the mediastinum and the hilum of the lungs were observed (Fig. 1B-D). A positron emission tomography (PET)/CT scan demonstrated different uptake values in a cavity in the apex of the right lung, a mass in the right upper lobe and a nodule in the right middle lobe, with maximum standardized uptake values (SUVmax) of 4.9, 16.2 and 6.8, respectively (Fig. 2A-C). Based on imaging findings, lung cancer and/or inflammatory disease, such as mycobacterial infection was suspected.

Although transbronchial biopsy of a mass adjacent to the pleura in the right upper lobe yielded no malignant cells, the acid-fast bacilli (AFB) smear tests of both sputum and bronchial lavage fluid from a cavitary lesion in the apex of the right lung were positive. While polymerase chain reaction tests for *M. tuberculosis* and MAC were negative, AFB was successfully cultured after two weeks in the mycobacterium growth indicator tube (MGIT) system and *M. heckeshornense* was finally identified with the matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF MS). Since the patient met the American Thoracic Society/Infectious Diseases Society of America diagnostic criteria of NTM-LD (11), a diagnosis of pulmonary *M. heckeshornense* infection was made, and we initiated treatment with RFP (300 mg/day), EB (750 mg/day) and CAM (800 mg/day) according to previous reports (1, 7). After one month of triple anti-mycobacterial therapy, the patient had converted to negative cultures, and we confirmed good drug susceptibility results of the isolated strain (Table 2). His symptoms and radiological findings improved (Fig. 3A, B) and mycobacterial cultures remain negative after nine months of treatment without any adverse events.

Since the possibility of coexistence of primary lung cancer with NTM-LD could not be excluded, we performed CT-guided transthoracic needle biopsy of a mass adjacent to the pleura in the right upper lobe, and the histological examination revealed adenocarcinoma. We clinically determined that a nodule in the right middle lobe was ipsilateral pulmonary metastasis, because it enlarged even under triple anti-mycobacterial therapy. Then, the clinical stage of lung cancer was classified as stage IIIA (cT4N0M0). Immunohistochemistry detected programmed cell death ligand 1 (22C3) expression in 5% of tumor cells, although the tumor did not exhibit any driver mutations, such as epidermal growth factor receptor gene mutations and anaplastic lymphoma kinase gene rearrangement. Considering multiple comorbidities and patient's wishes, a combined chemotherapy with CBDCA (area under the blood concentration time curve of 5), PEM (500mg/m^2) and pembrolizumab (200 mg/body) rather than surgery or chemoradiotherapy was commenced two-months after an anti-mycobacterial treatment initiation. A chest CT revealed shrinkage of a mass adjacent to the pleura in the right upper lobe and a nodule in the right middle lobe (27% reduction

Table 1. Laboratory data on admission.

Hematology			Biochemistry					
WBC	8900	/μL	AST	16	U/L	CRP	0.34	mg/dL
Neutro	60.5	%	ALT	10	U/L	ESR	20	mm/h
Lymph	30.3	%	ALP	98	U/L	BS	153	mg/dL
Mono	5.3	%	LDH	159	U/L	HbA1c (NGSP)	6.4	%
Eos	3.3	%	γ-GTP	14	U/L	PT	11.8	secs
Baso	0.6	%	CK	96	U/L	PT-INR	0.96	
RBC	462×10^4	/μL	T-bil	0.4	mg/dL	APTT	33.5	secs
Hb	14.2	g/dL	TP	7.4	g/dL	CEA	5.6	ng/mL
Ht	43.8	%	Alb	4.1	g/dL	CYFRA 21-1	2.4	ng/mL
Plt	34.9×10^4	/μL	T-cho	222	mg/dL	ProGRP	42.5	ng/mL
			TG	99	mg/dL	β-D-glucan	<6.0	pg/mL
			LDL-cho	136	mg/dL	*Aspergillus* Ag	0.2	
			Amy	59	U/L	Anti-MAC Ab	<0.5	U/mL
			BUN	15.2	mg/dL	T-SPOT.TB	(+)	
			Cre	0.73	mg/dL	ESAT-6	21	
			Na	142	mEq/L	CFP10	7	
			K	4.5	mEq/L			
			Cl	103	mEq/L			
			Ca	9.1	mg/dL			

ESR, erythrocyte sedimentation rate ; CEA, carcinoembryonic antigen ; CYFRA 21-1, cytokeratin fraction 21-1 ; ProGRP, pro-gastrin-releasing peptide ; *Aspergillus* Ag, *Aspergillus* galactomannan antigen ; Anti-MAC Ab, anti-M. avium complex antibody

based on Response Evaluation Criteria in Solid Tumors version 1.1) (Fig. 3A, C, D) after four cycles of chemotherapy without any severe adverse events. Thereafter, the patient continues triple anti-mycobacterial therapy and maintenance chemotherapy with no recurrence of pulmonary *M. heckeshornense* infection and lung cancer.

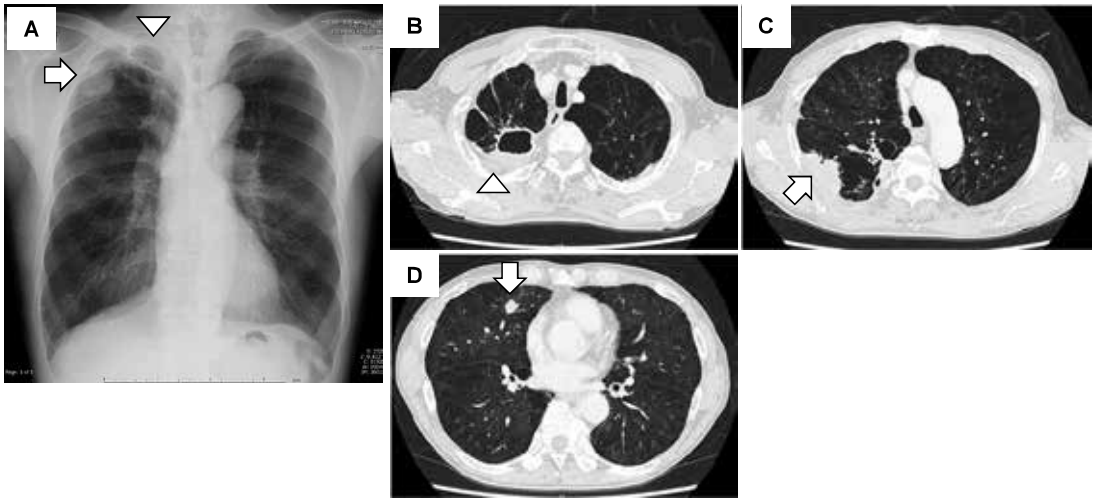

Figure 1. Images of chest X-ray and chest CT scan on admission. A chest X-ray revealed a cavitation with pleural thickening and a mass in the right upper lung field (A). A chest CT scan showed a cavity with a thick wall in the right apical region (B), a mass adjacent to the pleura in the right upper lobe (C), and a nodule in the right middle lobe (D). Arrowheads and arrows indicate the locations of pulmonary *M. heckeshornense* infection and lung adenocarcinoma, respectively.

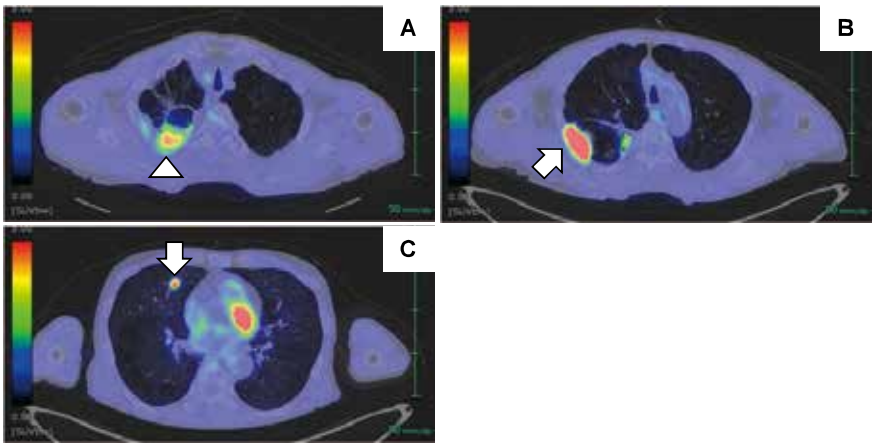

Figure 2. Findings of PET/CT scan on admission. A PET/CT scan revealed high uptakes in a cavity in the apex of the right lung (A), a mass in the right upper lobe (B) and a nodule in the right middle lobe (C), with SUVmax of 4.9, 16.2 and 6.8, respectively. Arrowhead and arrows indicate the locations of pulmonary *M. heckeshornens*e infection and lung adenocarcinoma, respectively.

Table 2. Results of the drug susceptibility test of isolated *M. heckeshornense* strain.

Drug	Minimal inhibitory concentration (μg/mL)	Interpretation
Streptomycin	≤0.06	Susceptible
Ethambutol	4	Intermediate
Kanamycin	≤0.06	Susceptible
Rifampin	≤0.03	Susceptible
Rifabutin	≤0.008	Susceptible
Levofloxacin	0.12	Susceptible
Clarithromycin	≤0.03	Susceptible
Ethionamide	4	Intermediate
Amikacin	≤0.5	Susceptible

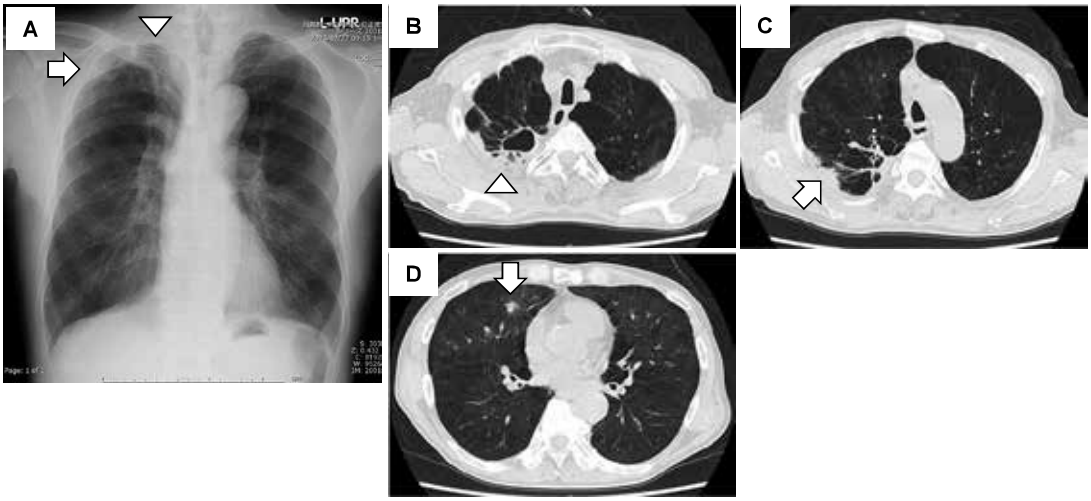

Figure 3. Images of chest X-ray and chest CT scan after treatments for pulmonary *M. heckeshornense* infection and lung adenocarcinoma. Radiological findings of the lesions of pulmonary *M. heckeshornense* infection (arrowheads) and lung adenocarcinoma (arrows) improved in chest X-ray (A) and chest CT (B-D).

DISCUSSION

M. heckeshornense is a rare, slow growing NTM categorized as Runyon group II, and often grows only in MGIT, not on solid medium (6). Since *M. heckeshornense* can be misidentified as *M. xenopi* in DNA-DNA hybridization methods (12), DNA sequence analysis of 16S ribosomal RNA used to be necessary for identification (13). However, the MALDI-TOF MS system has recently started being used commercially and is reliable in identifying *M. heckeshornense* species (14). In the present case, we could successfully identify *M. heckeshornense* with the MALDI-TOF MS system highlighting its clinical usefulness. The recommended treatments have not been established for pulmonary *M. heckeshornense* infection, because of its rarity (1, 6, 12-14), however, isolated *M. heckeshornense* strains have been shown to be resistant to isoniazid, but susceptible to RFP, EB, CAM, streptomycin, kanamycin, levofloxacin and ciprofloxacin (1, 12), which was consistent with results of the drug susceptibility test of isolated *M. heckeshornense* strain in the present case (Table 2). We initiated treatment with RFP, EB and CAM by reference to aforementioned drug susceptibility and a previous report (6). We also referred to previous therapeutic outcomes of pulmonary *M. xenopi* infections due to similar pathogenicity and clinical features between *M. heckeshornense* and *M. xenopi* (15). His symptoms and radiological findings improved and mycobacterial cultures have converted to negative, indicating the efficacy of our selected regimen.

Previous studies showed co-incidence of NTM-LD and lung cancer (7, 9). Axson *et al*. demonstrated that risk factors strongly associated with an increased likelihood of NTM included lung cancer (odds ratio 14.9 ; 95% confidence interval 3.98-55.7) in the adjusted model (8). Chronic pulmonary inflammation caused by NTM-LD is a plausible factor for the development of lung cancer (7), although the pathogenesis remains to be elucidated. The incidence of NTM-LD occurring in association with lung cancer will probably increase due to an increment in the incidence of both diseases. A retrospective study of 29 patients diagnosed as NTM-LD in combination with lung cancer demonstrated the most common lung cancer histology was adenocarcinoma (62.1%). The pathogens of NTM-LD in 31.0% of cases were *M. avium* and *M. intracellulare*, and in 13.8% of cases, *M. kansasii* and *M. gordonae* (10), however, coincidence of *M. heckeshornense* and lung cancer has never been reported before. To the best of our knowledge, this is the first report of pulmonary *M. heckeshornense* infection coexisted with lung cancer.

Although a SUVmax of ≥ 2.5 in PET/CT has been considered to be associated with malignant pulmonary nodules (16), Demura *et al*. showed that the mean value of SUVmax in 47 cases of NTM-LD was 5.1 (range, 2.5-7.6) (17). Similarly, the values of SUVmax of four NTM-LD lesions were reported to be moderately high (mean, 4.9 ; range, 3.6-7.8) (18). In the present case, a SUVmax of the lesion of pulmonary *M. heckeshornense* infection (a cavity in the apex of the right lung) was 4.9. These findings suggest that PET/CT may not be able to provide additional information to help differentiation of NTM-LD from lung cancer.

Anti-mycobacterial drugs, such as RFP and CAM, exhibit several effects on drug interactions, which can cause serious problems. The main cross-reactive effect of these drugs is the result of altered activity of cytochrome P450 enzyme (10). The serum concentration of drugs for treating lung cancer, including etoposide, irinotecan, docetaxel, paclitaxel, vinorelbine, gefitinib, erlotinib, afatinib and lorlatinib have the potential to change by the interactions with RFP and/or CAM (10). In previous reports of coexisting lung cancer and NTM-LD, almost all patients who received anti-cancer chemotherapy for lung cancer were not initiated anti-mycobacterial treatment for NTM-LD due to a concern about drug interactions (10, 19, 20), although whether NTM-LD should be treated during anti-cancer chemotherapy remains controversial. In the present case, we carefully selected a combined chemotherapy with CBDCA, PEM and pembrolizumab for treatment of lung adenocarcinoma, because any interactions with RFP and CAM have not been reported in these drugs. Although tumor shrinkage was achieved without any severe adverse events, much attention should be paid to the decreasing anti-tumor effect and increasing adverse events of anti-cancer drugs during anti-mycobacterial treatment for NTM.

In conclusion, we experienced the first case of pulmonary *M. heckeshornense* infection coexisted with lung cancer. An anti-mycobacterial treatment and a combined chemotherapy were fairly successful for pulmonary *M. heckeshornense* infection and primary lung adenocarcinoma, respectively. These observations indicated that triple anti-mycobacterial therapy with RFP, EB and CAM may contribute to good controls of *M. heckeshornense*

infection and that careful selection of anti-cancer drugs against lung cancer might be lead to favorable outcomes even during the course of anti-mycobacterial treatment.

CONFLICT OF INTEREST DISCLOSURE

Y.N. received research funding from Eli Lilly Japan K.K., and honoraria and paid expert testimony from MSD K.K. The other authors declare no conflicts of interest associated with this work.

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