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Case Report

Secondary spontaneous pneumothorax in a patient with resistant *Mycobacterium abscessus* infection and systemic sclerosis-associated interstitial lung disease: A case report

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ABSTRACT

Mycobacterium abscessus subsp. *abscessus* (MABA) is refractory and sometimes fatal especially in an immunocompromised patient. Also, MABA-associated pneumothorax is an extremely rare complication. We report a case of MABA pulmonary infection complicated pneumothorax treated successfully. A 69-year-old Japanese female with immunosuppressed systemic sclerosis-associated interstitial lung disease experienced left-sided secondary spontaneous pneumothorax. MABA was detected in the pleural effusion and blood culture. Microbial sensitivity test showed the MABA was sensitive to only amikacin, sitafloxacin, and clofazimine. Combination therapy with these antibiotics including azithromycin achieved remission within three weeks. In the treatment of MABA infection, compliance with microbial sensitivity test is crucial.

1. Introduction

Mycobacterium abscessus complex is one of nontuberculous mycobacteria (NTM) with an increasing prevalence in Japan [1,2]. The incidence of NTM pulmonary diseases caused by *Mycobacterium abscessus* complex is 3–4% in Japan [3]. Among these, *Mycobacterium abscessus* complex-associated pneumothorax is relatively rare [4–6], however, it is life-threatening and crucial issue especially for immunocompromised patients [7–9]. *Mycobacterium abscessus* complex treatment should be based on susceptibility, and a multidrug regimen should include at least three active drugs because of the variable and limited *in vitro* drug susceptibility [10]. *Mycobacterium abscessus* complex is divided into three subspecies: *M. abscessus* subsp. *abscessus* (MABA), *M. abscessus* subsp. *bolletii,* and *M. abscessus* subsp. *massiliense* [10]. Among these, MABA usually has a functional erythromycin ribosomal methylase (*erm*) gene (41), that confers macrolide-induced resistance and recalcitrance [11]. We report a successful treatment case of secondary spontaneous pneumothorax complicated with MABA infection in a patient with immunosuppressed systemic sclerosis-associated interstitial lung disease (SSc-ILD) with clofazimine (CLF) containing multidrug regimen without surgical procedure.

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2. Case presentation

A 69-year-old Japanese female had acute chest pain and dyspnea after coughing. She was diagnosed with SSc-ILD at the age of 50 years. The patient's SSc-ILD activity was relatively high that she was initially treated with several intravenous cyclophosphamides and maintenance therapies consisting of oral prednisolone at 10 mg/day though her serum Krebs von den Lungen-6 (KL-6) level ranged from 2000 to 3000 (IU/mL) as usual. The patient's lung function was poor and she also had pulmonary hypertension. According to her nearly 20-years history of prednisolone-dependent therapy, she was immunosuppressed as her CD4 level had been reduced to $<500/\mu L$.

She had low-grade fever of 37.9 °C, high blood pressure of 162/108 mmHg, tachycardia of 112/min, tachypnea of 28/min, and hypoxemia. She required 10 L/min of oxygen by a face mask to maintain oxygen saturation to 98 %. On examination, her respiratory sound diminished on the left side of the thorax. She had sausage like swelling and dermal sclerosis of fingers. Laboratory finding revealed leukocytosis (13,700/μL) with 85.7 % granulocytes without elevated C-reactive protein level (0.29 mg/dL). Lactate dehydrogenase (296 IU/L) and serum KL-6 (2498 IU/mL) levels were elevated, although the level of KL-6 was not different from that before her hospital visit. Chest X-ray revealed left-sided pneumothorax with a 55 % of collapse rate (Fig. 1a), and thoracic drainage was performed. Chest computed tomography (CT) after thoracic drainage showed traction bronchiectasis and honeycomb appearance in bilateral lower lungs with ground-glass opacity (Fig. 1b and c). Based on these CT findings, we suspected acute exacerbation of SSc-ILD complicated with pneumonia at first. Fig. 1Despite the treatment against acute exacerbation of SSc-ILD complicated with pneumonia, air leakage from the thoracic tube did not improve. Moreover, MABA was detected in the four bottles of blood culture and also from the pleural effusion within a four-days of culture period. We made a diagnosis of secondary spontaneous pneumothorax complicated with MABA infection. Then, imipenem/cilastatin (IPM/CS) 2g/day, amikacin (AMK) 500 mg/day (10 mg/kg) and azithromycin (AZM) 250 mg/day were started, however, the air leakage from thoracic tube continued. The microbial sensitivity test and minimum inhibitory concentrations (MICs, Brosmic RGM®, Kyokuto pharmaceutical INC, Tokyo, Japan) showed that her MABA was sensitive to only AMK, CLF, and sitafloxacin (STFX, mean MICs of 16, 0.5, and 2 μg/mL, respectively), but resistant to other drugs, including IPM/CS and macrolides (mean MICs of 32 and ≥64 μg/mL, respectively). IPM/CS was discontinued and oral CLF 100 mg/day and STFX 200 mg/day were added on 49th day of admission. As CLF was not approved for a treatment against MABA in Japan at this point, written informed consent was taken from the patient. AMK was discontinued on 61st day of admission because of auditory disturbance, but CLF, STFX, and AZM were continued. AZM was not sensitive, however, continued for its immunomodulatory property according to clinical guideline recommendation [10]. After pleurodesis by 50 mL of blood, the air leakage from thoracic tube stopped, and the tube was removed. She was discharged without relapse of pneumothorax on 73rd day of admission. Sequencing analysis detected the *erm*(41) gene in the MABA. Also, the patient's *Mycobacterium abscessus* complex was identified as MABA by multiplex polymerase chain reaction (Fig. 2). Moreover, her serum KL-6 level decreased gradually to 700–800 U/mL after MABA treatment.

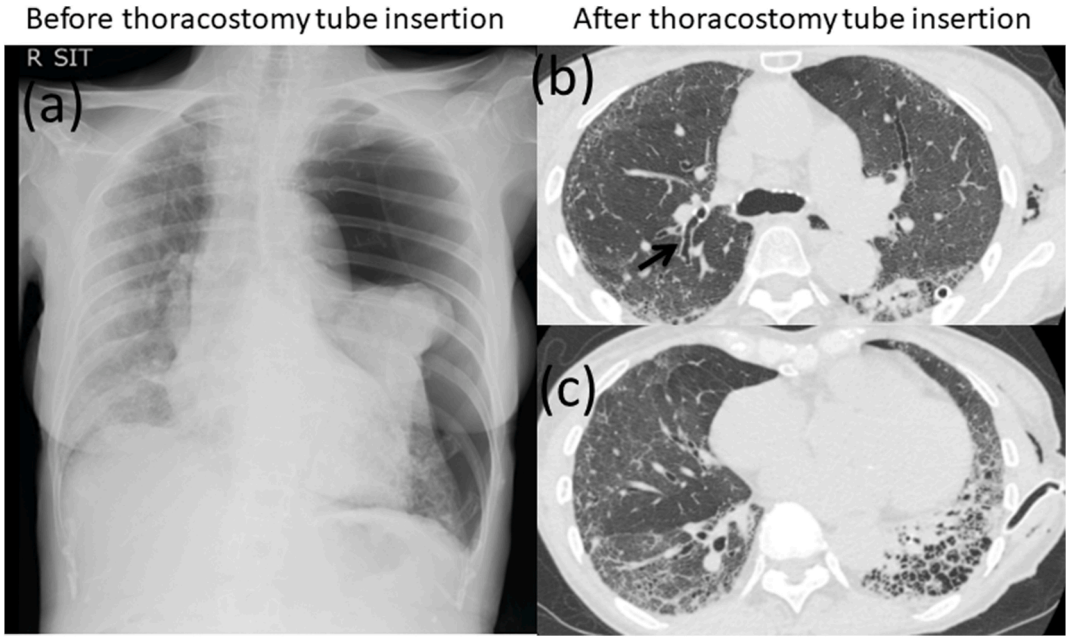

Fig. 1. Radiological findings on admission. (a) Chest radiograph on admission shows left-sided pneumothorax with collapsing rate of 55 %. (b, c) Computed tomography after insertion of thoracostomy tube shows traction bronchiectasis (arrow), ground-glass opacity (b) and honeycomb appearance on bilateral basal lungs (c). Multiple consolidations were also seen in subpleural lesions (b, c).

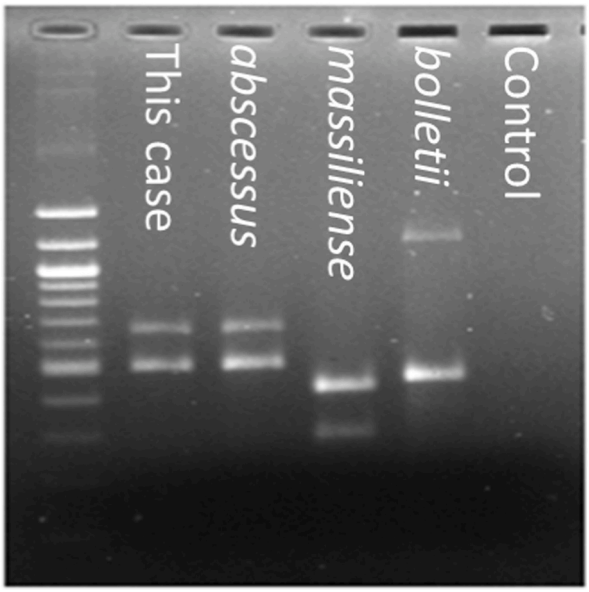

Fig. 2. Multiplex polymerase chain reaction testing of this patient.
Multiplex polymerase chain reaction testing by pleural effusion identified *Mycobacterium abscessus* subsp. *abscessus*.

2.1. Discussion

In this current report, we described a successful treatment case of secondary spontaneous pneumothorax complicated with MABA infection in a patient with immunosuppressed SSc-ILD with CLF containing multidrug regimen. Firstly, NTM-associated pneumothorax is a rare manifestation occurring 0.6–4.1 % of NTM pulmonary disease [4–6]. As more than 70 % of NTM-associated pneumothorax is caused by *M. avium-intracellulare* complex [4–6], MABA is extremely rare, and there were only four cases including the present case as far as we know (Table 1) [7–9]. Among these cases, a 56-year-old male with rheumatoid arthritis with immunosuppressant treatment had died [7], a 38-year-old female with tetralogy of Fallot induced by *Mycobacterium abscessus* subsp. *massiliense* showed no improvement after 6 months of therapy [8], and a 71-year-old male with bronchiectasis required bullectomy [9]. In the present case, we were not able to perform lung biopsy because it was too risky for this patient considering her lung function. It was not clear whether the pneumothorax was induced by MABA or it occurred as a complication of SSc-ILD. However, it was clear that the patient had a MABA pulmonary infection, and the pneumothorax was deteriorated as a result of the MABA pulmonary infection. Although the patient was thought to have had a less favorable prognosis, the pneumothorax improved after treatment using multi-drug combination therapy based on the results of the microbial sensitivity test successfully.

Secondly, *Mycobacterium abscessus* complex infection can be a refractory infection due to its variable and limited drug sensitivity [10]. Its main mechanism of resistance was the macrolide-mediated induction of the *erm*(41) gene [11]. MABA usually harbors an *erm* (41) gene, that confers macrolide-induced resistance and recalcitrance [11]. In this case, we treated the patient by using CLF containing multi-antimicrobial agents. CLF has been approved for a treatment against MABA since 2022 in Japan. CLF is a prototype riminophenazine antibiotic with *in vitro* activity against most mycobacteria, including *M. leprae*, multidrug-resistant *M. tuberculosis* and MABA. MABA has been reported to have excellent *in vitro* susceptibility to CLF because only 16 % of MABA isolates were resistant to it [12]. Moreover, the synergistic activity between CLF and AMK was documented in MABA treatment *in vitro* [13]. Hence, CLF is a promising antibacterial drug for treating MABA infections with a low drug-resistance rate, and synergic effect via combination ther-

Table 1
Reported cases of *Mycobacterium abscessus* complicated pneumothorax.

	Complication	Immunosuppressants	subsp.	Sensitive Drugs	Treatment	Surgery	Prognosis
56, M [7]	rheumatic arthritis	+	ND	CFX, AMK, KM, CAM, AZM	CFX + AMK + CAM	–	**Dead**
38, F [8]	tetralogy of Fallot	–	*massiliense*	CPFX, AMK, LZD, CAM	IPM/CS + AMK + AZM →LVFX + DOXY + AZM	–	**Unchanged**
71, M [9]	bronchiectasis	–	ND	ND	RFP + EB + CAM →MEPM + PZFX + CAM	+	Improved
69, F This case	systemic sclerosis, interstitial lung disease	+	*abscessus*	STFX, AMK, CLF	IPM/CS + AMK + AZM →STFX + AMK + CLF + AZM	–	Improved

Abbreviations. AMK, amikacin; AZM, azithromycin; CAM, clarithromycin; CFX, cefoxitin; CLF, clifazimine; CPFX, ciprofloxacin; DOXY, doxycycline; EB, ethambutol; F, female; IPM/CS, imipenem/cilastatin; KM, kanamycin; LVFX, levofloxacin; LZD, linezolid; M, mele; MEPM, meropenem; ND, not described; PZFX, pazufloxacin; RFP, rifampicin; STFX, sitafloxacin.

apy. In the present case, we treated the patient with a CLF containing regimen combined with AMK, AZM, and STFX, which resulted in a good outcome.

Furthermore, the patient's serum KL-6 levels decreased gradually to 700–800 U/mL from 2498 U/mL after MABA treatment. Serum KL-6 levels ≥2000 U/mL in patients with idiopathic pulmonary fibrosis are known to have higher risk of chronic lung infection, including NTM [14]. Moreover, serum KL-6 levels are associated with disease progression and treatment response in *M. avium-intracellulare* complex lung disease patients [15]. These reports indicate that a decline of serum KL-6 levels after MABA treatment may reflect MABA infection activity, and serum KL-6 levels may be associated with disease progression and treatment response in patients with MABA lung disease as well.

In conclusion, we have described a successful treatment case of secondary spontaneous pneumothorax complicated with MABA infection in a patient with immunosuppressed SSc-ILD with CLF containing multidrug regimen. The use of multi-antimicrobial agents based on microbial sensitivity test results is important in MABA infection treatment.

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Declaration of competing interest

The authors declare that they have no known competing financial interests in this case report.

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