Combination treatment with antibiotics and surgical lung resection for *Mycobacterium abscessus* pulmonary infection in a breast cancer patient

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**A R T I C L E   I N F O**

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**A B S T R A C T**

A 51-year-old woman was admitted to our hospital because of pneumonia after chemotherapy with doxorubicin and cyclophosphamide for left breast cancer. The patient was diagnosed with *Mycobacterium abscessus* pulmonary infection by the detection of *M. abscessus* complex (MABC) in sputum cultures. However, MABC is intrinsically resistant to most of the antibacterial agents, and MABC pulmonary disease outcomes with modern antibiotic treatment are currently the worst among all mycobacterial species. We herein report the successful treatment of *M. abscessus* pulmonary infection by a combination treatment with antibiotics and surgical lung resection.

1. Introduction

*Mycobacterium abscessus* complex is a species of nontuberculous mycobacterium (NTM) classified as a rapidly growing mycobacterium (RGM), class IV in the Runyon classification. *M. abscessus* infections account for approximately 3.3% of pulmonary NTM disease, which is the third-most frequent in Japan after *Mycobacterium avium/intracellulare* complex (MAC) (86.8%) and *M. kansasi* (4.3%) infections [1].

*M. abscessus* complex (MABC) is naturally resistant to many antibiotics and rapidly acquire drug resistance. At present, there is no dependable antibiotic regimen, including parenteral agents, to cure for *M. abscessus* pulmonary infection [2]. Curative therapy for *M. abscessus* lung disease is more likely to be obtained with antibiotics and, in the case of limited disease, a combination of surgical resection of the involved lung [3].

We herein report the successful treatment of *M. abscessus* pulmonary infection in a breast cancer patient by a combination treatment with antibiotics and surgical lung resection.

2. Case report

In July 2016, a 51-year-old woman was referred to our hospital because of chest abnormal shadows (Fig. 1A). Chest computed tomography (CT) showed small nodular shadows and bronchiectasis in the right upper lobe (Fig. 2A). Sputum cultures did not show any bacterial growth. She was followed up taking chest CT every half a year, which showed radiological stabilization until July 2018. Therefore, we viewed the progress of her.

In November 2018, she was diagnosed with left breast cancer (cT1bN1M0, stage IIA) of menopausal status (Fig. 3). At the same time, sputum culture showed *M. abscessus* growth. The minimum inhibitory concentrations of the bacterial isolates reported for clarithromycin (CAM), levofloxacin (LVFX), and amikacin (AMK) were \( >32 \) \( \mu \)g/mL, \( >32 \) \( \mu \)g/mL, and \( >16 \) \( \mu \)g/mL, respectively (Broth MIC NTM, Kyokuto Pharmaceutical Industrial Co., Ltd). At the end of November 2018, she first received neoadjuvant chemotherapy with doxorubicin (60mg/m²) and cyclophosphamide (600mg/m²) as dose-dense chemotherapy. At 9 days after chemotherapy, she had high-grade fever that continued. Therefore, she was referred to our department at 12 days after...
chemotherapy. She was subsequently diagnosed with pneumonia in the right upper lobe and hospitalized (Fig. 1B). On admission, her vital signs were as follows: blood pressure, 135/81 mmHg; body temperature, 38.0 °C; respiratory rate, 15 breaths/min. Chest radiography revealed infiltration shadows in the right upper lung field. Chest CT revealed ill-defined consolidation with neighboring granular shadows in the right upper lobe (Fig. 2B) and small nodule shadows in the middle lobe. Acid-fast bacilli smear of the sputum showed positive results, and sputum culture showed *M. abscessus* growth; moreover, there was no evidence of infection of other general bacteria. The white blood cell count was 12.4 × 10^9/L, with 79.5% neutrophils, 15.5% lymphocytes, and 5.0% monocytes. The C-reactive protein was elevated to 6.25 mg/dL (normal range, 0–0.3 mg/dL). Empirical intravenous antibiotic therapy was initiated with sulbactam/ampicillin, but the infiltrating shadows in the right upper lung field expanded (Fig. 1C). She was then diagnosed with pneumonia by *M. abscessus* based on the appropriate diagnostic guidelines [2]. Later, *M. abscessus* subspecies *abscessus* or *bolletii* was found by multiplex PCR assay, which could not be further distinguished. At the 5th hospital day, the empirical antibiotic therapy was stopped, and she

Fig. 1. (A) Chest X-ray at first presentation showing subtle nodular infiltrates in the right middle lung field. (B) Chest X-ray showing infiltration shadows in the right middle lung field in the beginning of December 2018. (C) Chest X-ray showing the expansion of infiltrating shadows in the right upper lung after 4 days of empirical intravenous antibiotic therapy.

Fig. 2. (A) Chest computed tomography (CT) images at first presentation showing small nodular shadows and bronchiectasis in the right upper lobe. (B) Chest CT images showing ill-defined consolidation with neighboring granular shadows in the right upper lobe on the date of hospital admission. (C) Chest CT images showing reduction of the infiltrating shadows in the right upper lobe on the 29th hospital day.

Fig. 3. Image of 18 fluorine fluorodeoxyglucose positron emission tomography/computed tomography showing intense fluorodeoxyglucose accumulation in the left breast tumor and left axillary lymph node metastasis.

Fig. 4. Histological examination of the surgically resected specimen revealing granulomatous pneumatic lesions.
was started on intravenous AMK (1000 mg/day), imipenem/cilastatin (IPM/CS) (2000 mg/day), and oral CAM (800 mg/day) for the treatment of M. abscessus pulmonary infections. At the 10th hospital day, the dose of AMK was changed to 800 mg/day after therapeutic drug monitoring. At the 19th hospital day, ultrasonography revealed remarkable shrinkages of the left breast cancer and axillary lymph node metastasis. Considering that MABC is naturally resistant to many antibiotics, we gave up any further neoadjuvant chemotherapy with anthracycline-containing regimen and decided to additionally excise the lung infected with M. abscessus to aim for complete healing. After the triple antibiotics therapy, acid-fast bacilli smear of the sputum had been negative for three times, and chest CT on the 29th hospital day showed reduction of the infiltrating shadows in the right upper lobe (Fig. 2C). Right upper middle lobectomy was then performed on the 39th hospital day. Pathological examinations of the surgically resected specimen showed granulomatous pneumatic lesions (Fig. 4), but no bacteria by Ziehl-Neelsen staining; moreover, there was no evidence of a subsequent mycobacterial culture in the lung tissue. Following the first triple antibiotics therapy, secondary treatment with oral CAM (800 mg/day), sitafloxacin (STFX) (100 mg/day), and faropenem (FRPM) (900 mg/day) was started on the 45th hospital day. At the 51st hospital day, intravenous AMK with cefoxitin or IPM/CS for at least 2 weeks to several cycles.

3. Discussion

More than 50 species of RGM have been identified, of which more than one-third have been described as human pathogens [4,5]. MABC is considered to be one of the most virulent of the RGM group [6], and it causes a wide spectrum of human disease, most commonly pulmonary disease, although it can cause soft tissue disease, bone disease, and disseminated disease in immunocompromised hosts [2,7]. Overall, the radiographic pattern is similar to the nodular bronchiectatic form of MAC lung disease [3]. Jarand et al. reported that patients with M. abscessus lung disease have a high rate of previous and/or concurrent MAC coinfection (55%), suggesting a close relationship between the disorders [8].

MABC was divided into three subspecies, namely M. abscessus subsp. abscessus, M. abscessus subsp. massiliense, and M. abscessus subsp. bolletii [9]. In Japan, Harada et al. performed a molecular identification of 102 previous M. abscessus clinical isolates and investigated clinical differences between M. abscessus subsp. abscessus and M. abscessus subsp. massiliense [10]. The analysis results showed that 71% of the isolates belonged to M. abscessus subsp. abscessus, 26% to M. abscessus subsp. massiliense, and 3% to M. abscessus subsp. bolletii. Clinical and radiological findings were indistinguishable between the M. abscessus and M. massiliense groups. Multiplex PCR assay showed that the bacteria in our case could be M. abscessus subsp. abscessus or bolletii, but it was impossible to distinguish them beyond that. The clinical practice did not enable the subspecies identification by genome sequencing.

Although NTM lung diseases can occur in association with various malignancies, the effect of anticancer chemotherapy on NTM lung diseases had been unknown. However, patients receiving intensive anticancer chemotherapy tend to be immunosuppressed, and thus it would be possible for the patients to contract pneumonia or sepsis caused by NTM. Japanese retrospective studies revealed that 3%–15% of patients with MAC had malignancy [11,12]. Tsuji et al. reported that among 728 patients with NTM lung diseases, 29 (3.9%) had lung cancer [13]; moreover, deterioration of NTM lung disease occurred in 2 (28.5%) of 7 patients during the course of chemotherapy, and the NTM species were M. chelonae and M. intracellulare. Redelman-Sidi and Sepkowitz reviewed 59 pulmonary RGM infection cases that had cancers, and concluded that among the cases, 26 were caused by M. abscessus (44%), 14 by M. chelonae (24%), and 12 by M. fortuitum (20%) [14]; furthermore, 7 (23%) of 30 patients died because of RGM infection. As our patient was diagnosed with acute pneumonia caused by MABC after anticancer chemotherapy, it was necessary to aim for the healing of MABC lung disease, considering long-term anticancer treatment.

MABC is intrinsically resistant to most antibacterial agents [15], and the outcomes of MABC pulmonary disease with modern antibiotic treatment are currently the worst among all mycobacterial species [16]. MABC is usually susceptible to some parenteral agents (AMK, cefoxitin, and IPM/CS) and macrolides (CAM and azithromycin), and thus CAM is the cornerstone of therapy for MABC [2,17]. However, there are differences in how M. abscessus subspecies develop macrolide resistance. M. abscessus subsp. abscessus and M. abscessus subsp. bolletii can express erythromycin resistance methylase (erm) that modifies the ribosomal binding site for macrolides, thereby causing antibiotics resistance in the early stage of macrolide treatment, whereas M. abscessus subsp. massiliense cannot [18]. Therefore, the antibiotic treatment success rates of M. abscessus subsp. abscessus are less than 50%, contrasting the high treatment success rates (80%–90%) of M. abscessus subsp. massiliense infection [19–23]. At present, the American Thoracic Society/Infectious Diseases Society of America recommended a combination therapy of intravenous AMK with cefoxitin or IPM/CS for at least 2 weeks to several months followed by oral macrolide [24]. Our patient was first treated by a combination therapy with AMK, IPM/CS, and CAM for approximately 5 weeks, followed by a second oral combination therapy with CAM, STFX, and FRPM for 1.5 year. In Japan, a second combination therapy such as that in our case is recommended [25]. Regarding drug sensitivity, the MABC of our patient showed resistance to CAM and AMK, but its resistance to other used drugs is unknown. There is a possibility of clinical effectiveness of prescribed drugs with unidentified sensitivity in our patient.

The reported success rates of medical treatment were approximately 25–30% in patients with M. abscessus lung disease [8,19,26]. Therefore, adjuvant resectional surgery could be considered in patients with intractable NTM lung disease predominantly localized to one lung who can tolerate resectional surgery [27,28]. Jarand et al. reported that there were significantly more patients receiving surgical treatment than patients receiving antibiotics alone among those whose culture converted and remained negative for at least 1 year [8]. A recent re-analysis of the role of surgery as an adjuvant therapy revealed that partial lung resections, but not pneumonectomy, were associated with improved treatment success such as cure and completion, and that surgery performed after an initial culture conversion was more likely to produce good outcome than surgery performed without culture conversion [29].

In conclusion, M. abscessus pulmonary infection in our patient worsened after anticancer therapy for breast cancer, and we successfully cured this infection by a combination treatment with antibiotics and...
surgical lung resection.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

References

[1] H. Namkoong, A. Kurashima, K. Morimoto, et al., Epidemiology of pulmonary nontuberculous mycobacterial disease, Jpn. Emerg. Infect. Dis. 22 (2016) 1116–1117.

[2] D.E. Griffith, T. Aksamit, B.A. Brown-Elliott, et al., An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases, Am. J. Respir. Crit. Care Med. 175 (2007) 367–416.

[3] D.E. Griffith, W.M. Girard, R.J. Wallace Jr., Clinical features of pulmonary disease caused by rapidly growing mycobacteria. An analysis of 154 patients, Am. Rev. Respir. Dis. 147 (1993) 1271–1278.

[4] E. Tortoli, Impact of geneotypic studies on mycobacterial taxonomy: the new mycobacteria of the 1990s, Clin. Microbiol. Rev. 16 (2003) 319–354.

[5] N. Martin-Casabona, A.R. Bahrmand, J. Bennedsen, et al., Non-tuberculous mycobacteria: patterns of isolation. A multi-country retrospective survey, Int. J. Tubercul. Lung Dis. 8 (2004) 1186–1193.

[6] B. Petrini, Mycobacterium abscessus: an emerging rapid-growing potential pathogen, APMIS 114 (2006) 319–328.

[7] S.K. Shah, K.J. McAnally, L. Seoane, et al., Analysis of pulmonary non-tuberculous mycobacterial infecisons after lung transplantation, Transpl. Infect. Dis. 18 (2016) 585–591.

[8] J. Jarand, A. Levin, L. Zhang, G. Huitt, J.D. Mitchell, C.L. Daley, Clinical and microbiologic outcomes in patients receiving treatment for Mycobacterium abscessus pulmonary disease, Clin. Infect. Dis. 52 (2011) 565–571.

[9] E. Tortoli, T.A. Kohl, B.A. Brown-Elliott, et al., Emended description of Mycobacterium abscessus, Mycobacterium abscessus subsp. abscessus and Mycobacterium abscessus subsp. massiliense comb. nov, Int. J. Syst. Evol. Microbiol. 66 (2016) 4471–4479.

[10] K. Jacobson, R. Garacia, H. Libshitz, et al., Clinical and radiological features of Mycobacterium abscessus and Mycobacterium massiliense lung diseases, J. Clin. Microbiol. 50 (2012) 3556–3561.

[11] K. Morimoto, T. Nakagawa, T. Asami, et al., Clinico-microbiological analysis of 121 patients with pulmonary Mycobacteroides abscessus complex disease in Japan-An NTM-JRC study with RIT, Respir. Med. 145 (2018) 14–20.

[12] T. Tsuji, K. Tsuyuguchi, K. Tachibana, et al., Analysis of the impact of lung cancer treatment on nontuberculous mycobacterial lung diseases, Respir. Investig. 55 (2017) 45–50.

[13] T. Tsuji, K. Tsuyuguchi, K. Tachibana, et al., Analysis of the impact of lung cancer treatment on nontuberculous mycobacterial lung diseases, Respir. Investig. 55 (2017) 45–50.

[14] G. Redelman-Sidi, K.A. Sepkowitz, Rapidly growing mycobacteria infection in patients with cancer, Clin. Infect. Dis. 51 (2010) 422–434.

[15] R. Neszar, E. Cambau, J.M. Peyrat, A. Murray, B. Glégué, Mycobacterium abscessus: a new antibiotic nightmare, J. Antimicrob. Chemother. 67 (2012) 810–818.

[16] J.G. Pasipanodya, D. Oghbona, B.E. Ferro, et al., Systematic review and meta-analyses of the effect of chemotherapy on pulmonary Mycobacterium abscessus outcomes and disease recurrence, Antimicrob. Agents Chemother. 61 (2017) e01206–17.

[17] Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical Section of the American Lung Association, Am. J. Respir. Crit. Care Med. 156 (1997) S1–S25.

[18] J.E. Stout, R.A. Floto, Treatment of Mycobacterium abscessus: all macrolides are equal, but perhaps some are more equal than others, Am. J. Respir. Crit. Care Med. 186 (2012) 822–823.

[19] W.J. Koh, K. Jeon, N.Y. Lee, et al., Clinical significance of differentiation of Mycobacterium massiliense from Mycobacterium abscessus, Am. J. Respir. Crit. Care Med. 183 (2011) 405–410.

[20] J. Lyu, B.J. Kim, B.J. Kim, et al., A shorter treatment duration may be sufficient for patients with Mycobacterium massiliense lung disease than with Mycobacterium abscessus lung disease, Respir. Med. 108 (2014) 1706–1712.

[21] J. Park, J. Cho, C.H. Lee, S.K. Han, J.J. Yim, Progression and treatment outcomes of lung disease caused by Mycobacterium abscessus and Mycobacterium massiliense, Clin. Infect. Dis. 64 (2017) 301–308.

[22] W.J. Koh, B.H. Jeong, S.Y. Kim, et al., Mycobacterial characteristics and treatment outcomes in Mycobacterium abscessus lung disease, Clin. Infect. Dis. 64 (2017) 309–316.

[23] R. Diel, F. Ringhsaumen, E. Richter, T. Welte, K.F. Rabe, R. Loddenkemper, Microbiological and clinical outcomes of treating non-Mycobacterium avium complex nontuberculous mycobacterial pulmonary disease: a systematic review and meta-analysis, Chest 152 (2017) 120–142.

[24] M.R. Lee, W.H. Sheng, C.C. Hung, C.J. Yu, L.N. Lee, P.R. Hsueh, Mycobacterium abscessus complex infections in humans, Emerg. Infect. Dis. 21 (2015) 1638–1646.

[25] A. Kurashima, Treatment of relatively rare species nontuberculous pulmonary mycobacteriosis, Kekkaku 86 (2011) 923–932 (in Japanese).

[26] H.Y. Kim, Y. Kook, Y.J. Yu, et al., Proportions of Mycobacterium massiliense and Mycobacterium abscessus group isolates, J. Clin. Microbiol. 46 (2008) 3384–3390.

[27] D.E. Griffith, T.R. Aksamit, Therapy of refractory nontuberculous mycobacterial lung disease, Curr. Opin. Infect. Dis. 25 (2012) 218–227.

[28] T.R. Aksamit, J.V. Philley, D.E. Griffith, Nontuberculous mycobacterial (NTM) lung disease: the top ten essentials, Respir. Med. 108 (2014) 417–425.

[29] G.J. Fox, C.D. Mitnick, A. Benedetti, et al., Surgery as an adjuvant treatment for multidrug-resistant tuberculosis: an individual patient data metaanalysis, Clin. Infect. Dis. 62 (2016) 887–895.