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

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ABSTRACT

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) (88.8%) and *M. kansasii* (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. In May 2017, bronchoscopic examination was performed on the right B^3, and polymerase chain reaction (PCR) results of bronchial washing were positive for *Mycobacterium avium*. Acid-fast bacilli smear of the bronchial washing was negative and the culture revealed *Mycobacterium abscessus* growth. However, sputum cultures did not show any bacterial growth in 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 μg/mL, >32 μg/mL, and >16 μg/mL, respectively (Broth MIC NTM, Kyokuto Pharmaceutical Industrial Co., Ltd). At the end of November 2018, she first received neoadjuvant chemotherapy with doxorubicin (60mg/m^2) and cyclophosphamide (600mg/m^2) 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

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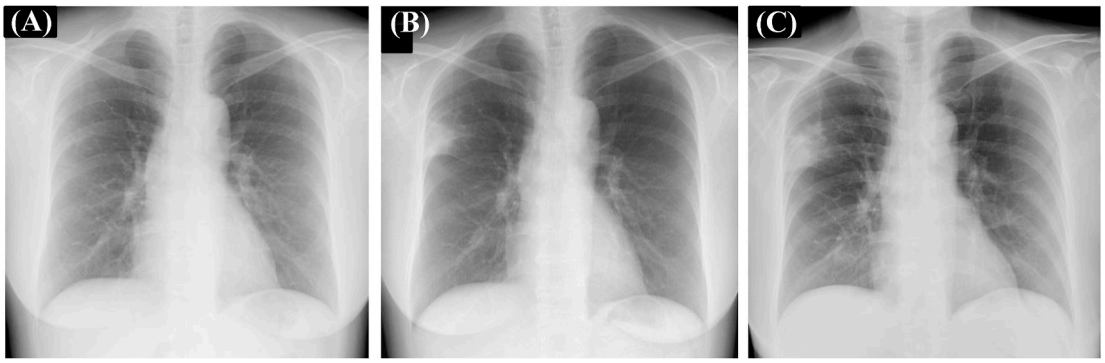

Fig. 1. (A) Chest X-ray at first presentation showing subtle nodular infiltrates in the right middle lung field. (B) Chest X-ray showing infiltration shadows in the right middle lung field in the beginning of December 2018. (C) Chest X-ray showing the expansion of infiltrating shadows in the right upper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

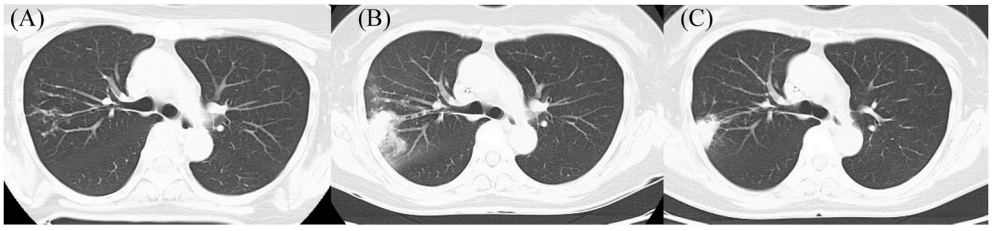

Fig. 2. (A) Chest computed tomography (CT) images at first presentation showing small nodular shadows and bronchiectasis in the right upper lobe. (B) Chest CT images showing ill-defined consolidation with neighboring granular shadows in the right upper lobe on the date of hospital admission. (C) Chest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

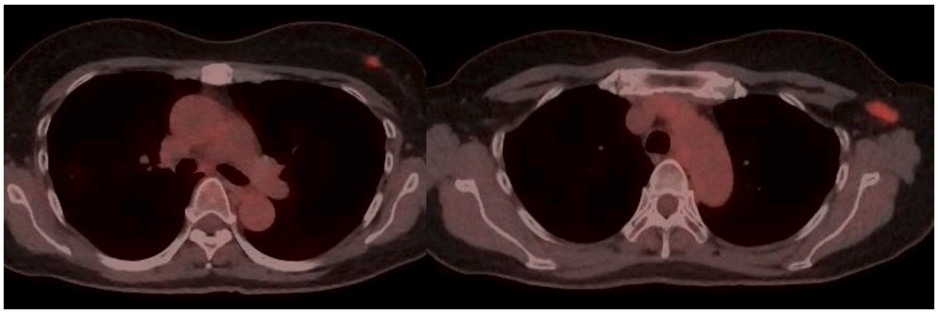

Fig. 3. Image of 18 fluorine fluorodeoxyglucose positron emission tomography/computed tomography showing intense fluorodeoxyglucose accumulation in the left breast tumor and left axillary lymph node metastasis.

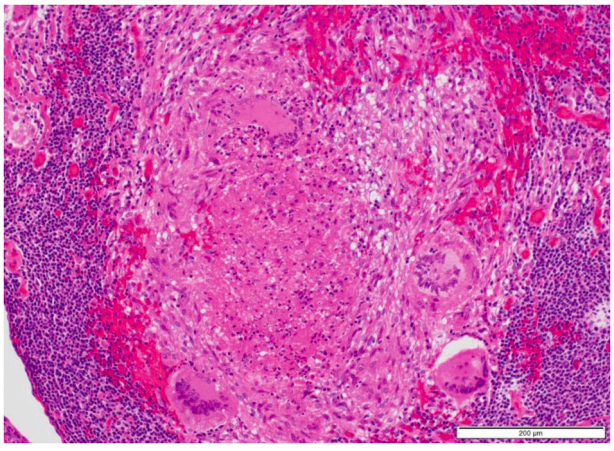

Fig. 4. Histological examination of the surgically resected specimen revealing granulomatous pneumonic lesions.

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 $\times$ 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

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 and was thought to be difficult to cure by antibiotics only, 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 pneumonic 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, left mastectomy with axillary lymph node dissection was performed, and the cancer was diagnosed as left HER2-positive breast cancer (ypT1aN1M0, ypstage IIA, Invasive ductal carcinoma, NG2, ER-negative, PgR-negative). At the 60th hospital day, the patient was discharged because her postoperative clinical course had been good. In mid-March 2019, she started adjuvant chemotherapy with a 3-week cycle of weekly paclitaxel (80 mg/m^2), which was continued for four cycles, trastuzumab (8 mg/kg as a loading dose, followed by 6 mg/kg intravenously every 3 weeks), and pertuzumab (840 mg as a loading dose, followed by 420 mg intravenously every 3 weeks), which was continued for a maximum of 18 cycles. At the third and fourth cycles of paclitaxel, the dose was reduced to 80% because of slight elevation of transaminase, which is categorized as grade 1 according to the Common Terminology Criteria for Adverse Events, version 4.0. Furthermore, from September 2019 to December 2019, trastuzumab and pertuzumab therapy had been stopped owing to decreased left ventricular ejection fraction to approximately 50%. Then, radiation therapy was administered to the remaining left breast for 60 Gy after four cycles of chemotherapy with paclitaxel. In May 2020, the patient had shown negative sputum cultures for *M. abscessus* for 18 months and stabile radiographic images, and thus the antibiotic treatment was finished. At the end of June 2020, trastuzumab and pertuzumab therapy was finished at 18 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 bronchiectasic 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. *massilliense* [10]. The analysis results showed that 71% of the isolates belonged to *M. abscessus* subsp. *abscessus*, 26% to *M. abscessus* subsp. *massilliense*, 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 MABC 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 resistantce 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 antibiotic alone among those whose culture converted and remained negative for at least 1 year [8]. A recent meta-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.

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