Introduction

*Mycobacterium avium* (*M. avium*) is the most frequently occurring pathogen among nontuberculous mycobacteria (NTM) that cause chronic lung infections in Japanese individuals [1]. *M. avium* is classified with *M. intracellularare* into *M. avium* complex (MAC), and the radiologic patterns of MAC are divided into five types on chest computed tomography (CT) imaging: nodular/bronchiectatic, fibrocavitary types, solitary pulmonary nodule, disseminated disease, and hypersensitivity-like disease [2]; however, infectious lung bullae are not included.

Lung bullae cause pneumothorax, bacterial infection, and intracystic bleeding in clinically progressed patients, but the bullae are rarely infected by *M. tuberculosis* or NTM other than *M. avium* [3–6].

Herein we report a rare case of pulmonary infected bulla caused only by *M. avium*.

Case report

A 37-year-old Japanese man with a smoking history of 30 pack-years was referred to our hospital for further evaluation and treatment of febrile chest pain with a niveau-like opacity in a bulla (10 × 10 cm) in the right upper lobe on chest CT. A chest radiograph obtained for a medical checkup one year previously showed lung bullae in the bilateral upper lung fields. In the previous hospital, pulmonary infectious bulla...
was suspected and meropenem (3 g/day) was administered for 9 days, followed by sulbactam/ampicillin (9 g/day) for 5 days, resulting in no symptomatic and radiological improvement. Physical examination on admission revealed the following: height, 179 cm; body weight, 48 kg; body temperature, 36.9°C; heart rate, 81 bpm; blood pressure, 110/70 mmHg; and oxygen saturation, 99% in room air. Chest auscultation demonstrated decreased breath sounds in the right upper lung field. No other abnormal physical findings were noted. The laboratory findings upon admission (Table 1) demonstrated an elevated peripheral blood platelet count (54.4 × 10^4/µl), peripheral blood white blood cell count (9800/µl), serum C-reactive protein level (10.89 mg/dl), and erythrocyte sedimentation rate (100 mm/hr). An interferon-gamma releasing assay performed for *M. tuberculosis* (QuantiFeron®) was negative; serum antigens specific for *Aspergillus*, *Cryptococcus neoformans*, anti-glycopeptidolipid (GPL)-core immunoglobulin A (IgA) antibody (also known as anti-MAC antibody), β-D glucan, and Krebs von den Lungen-6 (KL-6) were within normal limits.

No significant bacteria were detected in sputum smears; bacterial, fungal, and mycobacterial cultures and sputum cytology were negative. Chest radiography and CT upon admission revealed a pulmonary bulla with an air-fluid level in the right upper lung field (Fig. 1A); this bulla exhibited moderate intrabullous effusion (10 × 10 cm) in the right upper lobe of the emphysematous lung on chest CT (Fig. 1B).

After admission, doripenem (3 g/day) was administered for 5 days for suspected infected bulla caused by common bacteria, which resulted in increased intrabullous effusion and unaltered peripheral blood white cell count and C-reactive protein level, despite strong broad-spectrum antibiotic therapy. Next, because the infected bulla occupied nearly half of the right upper lobe and did not respond to broad-spectrum antibiotic therapy, right upper lobe lobectomy was performed for the treatment and evaluation of the causative pathogen. The bulla had tightly adhered to the chest wall and surrounding lung parenchyma, damaging the cyst wall and preventing en bloc resection of the infected bulla. En bloc resection was selected to prevent intrathoracic contamination of the pathogen by the intrabullous fluid. Macroscopic examination of the resected lung specimen revealed a giant bulla occupying half of the right upper lobe (10 × 10 cm) (Fig. 2A) with whitish areas in the lung parenchyma surrounding the bulla. No communications between the cyst and re-

### Table 1. Patient’s laboratory data upon hospital admission

| Blood cell counts | Blood chemistry | ESR | QFT (QuantiFeron®) | PT% | PT-INR | APTT |
|-------------------|-----------------|-----|--------------------|-----|--------|------|
| WBC 9800/µl       | TP 7.8 g/dl     | 100 mm/hr | negative | 64.6% | 1.26   | 45.3 second |
| Neutrophils 74.4% | Alb 3 g/dl      |      |                   |     |        |      |
| Lymphocytes 18.1% | T-bil 0.4 mg/dl |      |                   |     |        |      |
| Eosinophils 0.9%  | AST 25 IU/l     |      |                   |     |        |      |
| Monocytes 6%      | ALT 74 IU/l     |      |                   |     |        |      |
| Basophils 0.6%    | LDH 132 IU/l    |      |                   |     |        |      |
| RBC 3.92×10^4/µl  | ALP 368 IU/l    |      | *Aspergillus* antigen |     |        |      |
| Hb 11.9 g/dl      | γ-GTP 81 IU/l   |      | *Cryptococcus neoformans* antigen |     |        |      |
| Ht 35.8%          | BUN 15 mg/dl    |      |                   |     |        |      |
| Platelets 54.4×10^4/µl | Cre 0.61 mg/dl | <Coagulation> |     |        |      |

WBC: white blood cell, RBC: red blood cell, Hb: haemoglobin, Ht: haemocrit, TP: total protein, Alb: albumin, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transferase, BUN: blood urea nitrogen, CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, ESR: equivalent series resistance, GPL: glycopeptidolipid, IgA: immunoglobulin A, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time.
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Inspiratory tract were noted in the pathological findings. Microscopically, numerous multinucleated giant cells were observed in these areas that were positive for mycobacteria on Ziehl–Neelsen staining (Fig. 2B); the culture results of the intrabullous fluid were positive for M. avium and negative for bacteria; thus the patient was diagnosed with infected bulla caused by M. avium. After the surgery, serum C-reactive protein level promptly improved to 2.6 mg/dl and WBC improved to 6200/μl. In addition, treatment with rifampicin, ethambutol and clarithromycin was started on the 5th day after surgery. The serum level of C-reactive protein was normalized two months after the surgery and no relapse was observed for six months after the surgery.

Discussion

In a study conducted on giant lung bullae, the incidence of infected bullae was 10% [7], and the causative pathogens were generally common bacteria. Mycobacteria and fungi were also reported as causative pathogens of infected bullae, but their precise incidences were unknown [7]. In detecting causative pathogens of infected bullae, lost communications

Fig. 1. Image findings on admission. A: Chest radiograph upon admission, demonstrating a bullous lesion with a niveau-like shadow in the right upper lung field. B: Chest computed tomography upon admission, demonstrating a bulla (10 × 10 cm) with intrabullous effusion in the right upper lobe and emphysematous lung.

Fig. 2. Pathological findings. A: Macroscopic examination, demonstrating a giant bulla occupying half of the resected right upper lobe. B: Microscopic examination, demonstrating caseating epithelioid granuloma with Langhans giant cells (hematoxylin eosin stain).
with airways and intrabullous space may be linked to the low identification rate of the etiologic pathogens of infected bullae using sputum or bronchial washing samples [8]. It is challenging to speculate the infectious route of *M. avium* into the bullous space, but the process by which *M. avium* enters the intrabullous space and the subsequent inflammatory change in intrabullous effusion may be more plausible than the formation of cavitation with intracavitary effusion after mycobacterial infection in the lung parenchyma [5]. In our patient, bullae were noted in the bilateral upper fields on a chest radiograph one year previously; therefore, we speculated that the infected bulla occurred via the above-mentioned mechanism.

The mainstay of the treatment of infected lung bullae is appropriate systemic antibiotic therapy and respiratory tract drainage, and invasive procedures, including percutaneous drainage of intrabullous fluid and cystectomy, may be considered in patients with uncontrolled intrabullous infection. Percutaneous intrabullous drainage poses the risks of pneumothorax, hemothorax, and empyema [9], and careful discretion should be exercised.

Regarding the surgical treatment of pulmonary nontuberculous mycobacterial disease, the American Thoracic Society and Infectious Diseases Society of America stated that there is no evidence of the necessity of postoperative systemic antimycobacterial chemotherapy when surgical resection of pulmonary solitary nodule with a clear margin without peripheral spread is achieved [10]. However, whether systemic antimycobacterial treatment after the complete resection of infected bulla is necessary has not yet been established. Our patient was considered to be free of apparent intrathoracic mycobacterial infection after surgical resection, but postoperative systemic antimycobacterial chemotherapy was performed owing to possible intraoperative intrathoracic spread of pathogen to the infected bulla.

Interestingly, the patient was negative for serum anti-GPL-core IgA antibody. Hagiwara *et al.* reported that 64.5% (80/124) of patients with newly diagnosed pulmonary MAC disease were positive for serum anti-GPL-core IgA antibody, and the lower rate (33.3%) of patients with solitary pulmonary nodule classified by radiologic patterns are positive for the anti-GPL-core IgA antibody compared with all patients with MAC (47–84%) [11]. There are no reports on the rate of patients positive for serum anti-GPL-core IgA antibody in patients with pulmonary infected bulla caused by *M. avium* [6], and further accumulation of clinical data is required in such clinical situations.

There have been only a few reports of infected lung bullae caused by mycobacteria so far, partly because of the difficulty in detecting pathogens in the bulla. However, it is anticipated that the number of patients with infectious bulla caused by mycobacteria, as in the present case, will increase in the future due to an increase in the number of patients with pulmonary MAC disease [12]. Previously reported cases of mycobacterial infectious bullae showed only minimal inflammatory findings in laboratory data compared with those caused by common bacteria [6]; therefore, physicians should be aware of mycobacterial infection in infected bullae without systemic inflammatory reactions.

In conclusion, we reported a rare case of lung infected bulla caused by *M. avium* that was diagnosed via surgical treatment. Physicians should be aware that mycobacteria cause pulmonary infected bullae.

**Conflicts of Interest**

The authors declare no conflicts of interest in association with the present study.

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Mycobacterium avium による感染性肺嚢胞の一例

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要 旨：症例は、胸部レントゲン写真にて右上肺野にニボー様の透過性低下を伴った肺嚢胞を指摘された37歳の男性。広域スペクトラムの抗菌薬治療にも関わらず、液面レベルは徐々に上昇した。右上葉切除が行われ、抗酸菌を伴った類上皮肉芽腫が病理組織学的に認められた。内腔液の細菌培養検査は陰性であったが、抗酸菌培養検査は Mycobacterium avium が陽性であった。そのため、患者は Mycobacterium avium による感染性肺嚢胞と診断された。感染性肺嚢胞の切除後、患者は抗酸菌治療薬を用いた追加治療を受けた。我々が知る限り、本報告は、Mycobacterium avium によってのみ生じた感染性肺嚢胞の最初の英文報告である。

キーワード：非結核性抗酸菌症, 感染性肺嚢胞, 肺切除, Mycobacterium avium.

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