Congenital Cystic Adenomatoid Malformation in Adulthood Complicated by *Mycobacterium celatum* Infection

Satoshi Ikegame¹, Yoshinori Nagamatsu¹, Nobuhiko Nagata², Yuko Kazumi³,
Satoshi Mitarai³, Yasunori Iwasaki¹, Chika Harada¹, Hiroyuki Kumazoe¹,
Masayuki Kawasaki¹ and Akira Kajiki¹

Abstract

A 25-year-old woman with no underlying disease presented with a large fluid-filled cavitory lesion in the right lung. *Mycobacterium celatum* was isolated from the cavitory fluid, and treatment with ethambutol, rifampicin, and clarithromycin was initiated. After 4 months of treatment, right lower pulmonary lobectomy was performed. Histological examination confirmed *M. celatum* infection as well as concurrent congenital cystic adenomatoid malformation (CCAM). *M. celatum* has been implicated in opportunistic infections. This infection, however, was related to underlying CCAM, which resulted in a large cavitory lesion. CCAM diagnosed in adulthood is rare, and is made more challenging by an infectious complication.

Key words: non-tuberculous mycobacteriosis, *Mycobacterium celatum*, congenital cystic adenomatoid malformation

(Intern Med 51: 2203-2207, 2012)

(DOI: 10.2169/internalmedicine.51.7848)

Introduction

Advances in diagnostic and therapeutic technology in recent years have greatly contributed to elucidation of the pathogenesis of mycobacteriosis, as represented by tuberculosis. Infections with mycobacteria other than tubercle bacilli (non-tuberculosis mycobacteria: NTM) are essentially treated with uniform therapy (1). However, as the number of NTM strains identified to date exceed 100 (2), it is important to collect case studies on rare isolated bacterial strains in order to apply specialized knowledge to individual cases and provide appropriate treatment.

Here we report a healthy adult woman who developed a pulmonary infection with *Mycobacterium celatum* and was subsequently found to have congenital cystic adenomatoid malformation (CCAM). She underwent medical therapy, followed by surgical treatment. The significance of this case will be discussed in terms of the pathogenesis of *M. celatum* infection as well as complications of CCAM, along with

some literature review.

Case Report

The patient was a healthy 25-year-old woman with no previous indication of disease. In June 2011, a chest X-ray performed during a medical examination revealed a large cavitory lesion containing fluid in the right lung (Fig. 1A). She visited her previous doctor with right back pain one week later. Bronchoscopy was performed for suspected lung abscess, but no diagnosis was reached. She was referred to our hospital and admitted for close examination and treatment. She had no history of smoking or family history of particular disease. On auscultation, she was found to have weak breath sounds over the right lung base. Body temperature was 36.9°C. Blood sample test showed a mild inflammatory reaction with CRP level of 0.56 mg/dL, but no other abnormal findings were noted (Table 1).

A chest X-ray performed during a medical examination in 2010 revealed an area of increased lucency in the middle

¹National Hospital Organization, Omuta National Hospital, Japan, ²Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, Japan and ³Department of Mycobacterium Reference and Research, Research Institute of Tuberculosis, Japan

Received for publication March 28, 2012; Accepted for publication May 8, 2012

Correspondence to Dr. Satoshi Ikegame, ikegame-s@oomuta-h.com

Figure 1. Chest X-ray images at onset (A) and one year prior to onset (B).

Table 1. Laboratory Data on Admission

Complete blood cell count		Serum chemistry	
White blood cell	7,200 / μ L	Total protein	7.3 g / dL
Neutrophil	66.8 %	Albumin	3.9 g / dL
Eosinophil	3.0 %	AST	14 IU / L
Basophil	0.3 %	ALT	12 IU / L
Monocyte	4.7 %	γ -GTP	24 IU / L
Lymphocyte	25.2 %	LDH	138 IU / L
Red blood cell	434×10^4 / μ L	Glucose	90 mg / dL
Hemoglobin	11.8 g / dL	BUN	7 mg / dL
Hematocrit	35.5 %	Cr	0.56 mg / dL
Platelet	29.4×10^4 / μ L	Total cholesterol	172 mg / dL
Arterial blood gas (under room air condition)		Triglyceride	42 mg / dL
pH	7.411	Na	142 mEq / L
PaO ₂	94.1 Torr	K	4.4 mEq / L
PaCO ₂	42.4 Torr	Cl	110 mEq / L
HCO ₃ ⁻	26.3 mEq / L		
Base excess	1.5 mEq / L		
Immunology			
C-reactive protein	0.56 mg / dL	β -D-glucan	< 5 pg / mL
HBs antigen	negative	Candida antibody	negative
HCV antibody	negative	Aspergillus antigen	0.2 (negative)
TPLA	negative	Cryptococcus antigen	negative
HTLV-I antibody	negative	Quantiferon® TB 3G	< 0.10 IU / mL (negative) (control: 1.62 IU / mL)

lung and a reticular shadow in the middle exterior of her right lung, suggesting the presence of a cavitory lesion (Fig. 1B). Chest computed tomography (CT) scans obtained on admission revealed a large cavitory lesion containing fluid in the right lower lobe (Fig. 2A, B) and multiple microcystic (number: several tens, shape: circle to ellipse, diameter: 5 to 10 mm) lesions on the mediastinum side of the large cavitation (Fig. 2C). Following admission to our hospital, purulent secretions were collected via percutaneous paracentesis from the right lung abscess. The acid-fast stained smear was positive (2+), and PCR test was negative for both *Mycobacterium tuberculosis* and *Mycobacterium avium* complex (MAC).

It was suspected that the patient had some type of bullous lung disease complicated by NTM infection. As the patient strongly wished to be treated on an outpatient basis, therapy with ethambutol (EB) at 750 mg/day, rifampicin (RFP) at 450 mg/day, and clarithromycin (CAM) at 600 mg/day was

initiated without aminoglycoside administration. Subsequently, her right back pain disappeared, and the amount of cavity fluid decreased; however, achievement of permanent cure with medical therapy alone was deemed difficult, given that the patient had NTM infection with large cavitation (the bacterial strain was unidentified preoperatively).

Four months after the initiation of antibiotic therapy, open-chest lower right lobectomy was performed. Radial resection of the infected lesion was successful, with no particular postoperative complications. As indicated by her chest CT scans, a large cavitory lesion containing purulent fluid (92×60 mm) and multiple microcystic lesions (<1 cm in diameter) mainly distributed in the right lung near S¹⁰ were confirmed in the resected right lower lobe (Fig. 3A). Histopathological examination of the cavitory lesion (Fig. 3B) revealed granuloma consisting of Langerhans' giant cells and necrotic tissue, which was likely associated with known mycobacterial infections. The acid-fast stained

Figure 2. Plain chest CT scans on admission (B is the mediastinal image of A).

Figure 3. Resected, formalin-fixed lower right lung lobe (A). B and C are histopathological images (140-fold magnification and 14-fold magnification, respectively) of the enclosed area on A. D is a magnified image of the cyst wall on C (56-fold magnification).

smear of the purulent fluid obtained from the resected lung was positive (2+), and the culture test was also positive. There seemed to be little change in the bacterial content be-

fore or after treatment, because acid fast stained smear showed no difference before (2+) or after (2+) treatment; quantification of the isolated bacteria in the purulent fluid

Table 2. Minimum Inhibitory Concentrations of Drugs to Isolated *Mycobacterium celatum*

Streptomycin	0.5	μg/mL
Ethambutol	0.25	μg/mL
Kanamycin	1	μg/mL
Rifampicin	16	μg/mL
Rifabutin	0.25	μg/mL
Levofloxacin	0.125	μg/mL
Clarithromycin	0.03	μg/mL
Ethionamide	1	μg/mL
Amikamycin	0.5	μg/mL

could not be determined, because the exact volume of pus was not known. Histopathological examination of the multiple microcystic lesions (Fig. 3C) revealed that the cysts were covered by bronchiolar-type epithelium, with some areas also lined by the smooth muscle. A diagnosis of pulmonary sequestration was ruled out due to the lack of an abnormal artery originating from the aorta, and instead, a diagnosis of type II CCAM was given.

The isolated mycobacteria could not be identified by a DNA-DNA hybridization method using a DDH Mycobacteria kit (Kyokuto Pharmaceuticals, Tokyo, Japan), and efforts to identify the strain were carried out at the Research Institute of Tuberculosis (RIT, Tokyo, Japan). Sequence analysis of the *hsp65* and *rpoB* confirmed the identification of *M. celatum*. Since *M. celatum* infection has been associated with HIV infection (3), the presence of HIV antibody was inspected following the identification of the bacterial strain. However, the test for HIV antibody was negative. Given that mycobacterial drug susceptibility test (Table 2) showed low sensitivity to RFP and good sensitivity to levofloxacin (LVFX), postoperative chemotherapy with LVFX at 500 mg/day, in addition to EB, RFP, and CAM, will be continued until approximately 12 months post-operation according to the guideline of Japanese Society for Tuberculosis (4).

Discussion

In this report, we described a patient who developed lung abscess in the right lobe due to underlying CCAM complicated by *M. celatum* infection. The significance of this rare case is two-fold: first, the patient was found to have CCAM, which is usually diagnosed in childhood, when she developed mycobacterial infection; second, the infection with *M. celatum* occurred in association with underlying pulmonary lesions (CCAM), whereas in other countries, *M. celatum* infection has been closely associated with immunosuppression caused by HIV infection, etc.

CCAM is a cystic disease attributed to malformation of the lung and normally diagnosed prenatally or in early childhood (5). In rare cases, however, patients remain asymptomatic through childhood and receive the diagnosis later in life based on bloody sputum or due to complicating infections (6-8). Hellmuth et al. (9) reported 23 cases of

adulthood CCAM, 8 patients were found by repetitive pneumonia. The only adult-onset case associated with mycobacterial infection is that of tuberculosis (10). As in the present case, the diagnosis of CCAM can be difficult when the patient develops complicating mycobacterial infection that destroys lung tissue. In areas other than pediatrics where CCAM is not nearly as prevalent, this condition can be easily overlooked, unless uninfected regions are carefully inspected. Conversely, in the case of mycobacterial infection with multi- or huge-cystic lesions, careful pathological inspection is needed to ascertain the underlying cause of cystic disease. In the present case, it seemed that the cavitory lesion rapidly progressed within one year (Fig. 1A, B). The reason for this progression could be hypothesized as follows: (i) complicated *M. celatum* infection damaged the lung, (ii) check valve mechanism enlarged the cavity. Hypothesis (i) seemed less likely, because she had no symptom suggesting massive tissue destruction (such as fever, sputum, and hemoptysis). Although the cavity had no communication with bronchus by the inspection of surgically resected lung, *M. celatum* infection might mask the check valve mechanism.

Patients with pulmonary sequestration exhibit multiple microcystic lesions on imaging (11) and often present with pathological findings that include cysts lined by bronchiolar-type epithelium (12); therefore, differentiation from CCAM is often required. The presence of an abnormal artery originating from the aorta is the defining point of pulmonary sequestration. In the present case, the diagnosis of CCAM was given based on the fact that no abnormal vessels were found on CT images or by inspection of the surgical specimen. CCAM is classified by the site and size of cysts into types 0, I, II, III, and IV according to the revised Stocker's classification (13) (original classification (14) was classified into I, II, and III). The present patient was diagnosed as having type II CCAM based on the occurrence of multiple microcysts of less than 1 cm in diameter.

The standard therapy for adulthood CCAM is surgical resection of an affected lobe to prevent or control the complicated infections, if patients are tolerant for surgical resection (8). In addition, in the present case there was another reason for surgery; she had a NTM disease with a huge cavity and NTM was localized to one lobe. NTM (especially MAC) diseases with a huge cavity are related to the failure of antibiotic therapy (15).

M. celatum, a Runyon III mycobacterium (3) discovered in 1993, is rarely isolated as a causal bacterium for infection (16). In the United States, it is strongly implicated in opportunistic infections associated with HIV infection (7), although other cases do exist where preexisting pulmonary lesions underlie the development of infection in healthy individuals with normal immune function. This bacterium exhibits low sensitivity to RFP *in vitro* (MIC =128 μg/mL), with well-maintained sensitivity to new quinolones (MIC against ciprofloxacin =0.25-2 μg/mL, ofloxacin =0.12-2 μg/mL) (17) and amikacin (MIC =0.25-2) (17) and EB (67% of

isolates were $\leq$ MIC 5 $\mu\text{g/mL}$) (3). Combination therapy consisting of these drugs is thought to be effective, but this conclusion is not based on strong evidence *in vivo*. The bacteria we isolated also demonstrated a similar trend (RFP, MIC =16 $\mu\text{g/mL}$; LVFX, MIC =0.125 $\mu\text{g/mL}$), and decontamination was not achieved by the 4-month preoperative medical treatment. Although curative resection of the causal lesion was successful, the present patient is currently undergoing additional LVFX therapy, as we thought that the addition of LVFX might reduce the likelihood of recurrence. Identification of *M. celatum* may take a long time in the laboratory setting, as it cannot be identified by the DDH test; however, in practice clinical decisions often must be made before the identity of the pathologic bacteria is determined. We suspected that the isolated bacteria in the present case was a non-MAC NTM based on the result of PCR. The standard antibiotic regimen was not established before identification of the type of mycobacteria (1). Therefore, we decided to initiate antibiotic therapy according to MAC diseases (representative of NTM), referring to “infrequently encountered NTM” in ATS/IDSA guideline (1). Although conclusions should not be simply drawn based on a few pieces of evidence or *in vitro* data alone, early administration of LVFX should be considered in similar cases.

The authors state that they have no Conflict of Interest (COI).

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