Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6189-20
Intern Med 60: 3041-3045, 2021
http://internmed.jp

【 CASE REPORT 】

Bursitis, Bacteremia, and Disseminated Infection of *Mycobacteroides* (*Mycobacterium*) *abscessus* subsp. *massiliense*

Keisuke Oka[1], Hiroshi Morioka[1], Motoki Eguchi[2], Yoshitaka Sato[1,3], Nobuyuki Tetsuka[1], Mitsutaka Iguchi[1], Takeshi Kanematsu[4], Hanako Fukano[5], Yoshihiko Hoshino[5], Hitoshi Kiyoi[6] and Tetsuya Yagi[1]

Abstract:
We herein report a 59-year-old woman with a 2-year history of chronic bursitis of the hand who took 50 mg/day prednisolone for several autoimmune diseases. *Mycobacteroides abscessus* subsp. *massiliense* was isolated from the abscess and blood culture. Combination therapy (imipenem/cilastatin, amikacin, and clarithromycin) was administered for a month. Two months later, *M. massiliense* was detected from a blood culture again, and disseminated lesions were found. Clarithromycin and sitafloxacin were administered following eight weeks of the same regimen. Six months after the diagnosis, *M. massiliense* was isolated from a blood culture, and she expired due to multiple organ failure.

Key words: *Mycobacterium abscessus*, bursitis, bacteremia, disseminated infection

(Intern Med 60: 3041-3045, 2021)
(DOI: 10.2169/internalmedicine.6189-20)

Introduction

In Japan, the frequency of detection of nontuberculous mycobacteria (NTM) was reported to be in the order of *Mycobacterium avium-intracellulare* complex (MAC), *Mycobacterium kansasii*, and *Mycobacteroides* (*Mycobacterium*) *abscessus* complex (MABC) (1). In a recent Japanese report of NTM pulmonary diseases, MABC was the second-most frequently reported entity (2). MABC is a group of rapidly growing mycobacteria (RGM) that are resistant to drugs. MABC is classified into three subspecies: *M. abscessus* subsp. *abscessus* (*M. abscessus*), *M. abscessus* subsp. *bolletii* (*M. bolletii*), and *M. abscessus* subsp. *massiliense* (*M. massiliense*).

The number of RGM infections has been increasing in Japan, but reported cases of extrapulmonary RGM infections, including bacteremia caused by MABC, are still rare (3).

We herein report a case of chronic bursitis, recurrent bacteremia, and disseminated infections caused by *M. massiliense* in a patient treated with long-term prednisolone therapy.

Case Report

A 59-year-old Japanese woman visited our hospital because she noticed a mass on the back of her right hand. She had no history of trauma or soil exposure in her right hand. She had multiple underlying diseases of autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP) with splenectomy, and antiphospholipid antibody syndrome. She had been treated by rituximab, prednisolone 50 mg/day, and eltrombopag.

In June 20X(Y-2), she noted that her right opisthenar was swollen, and she had difficulty stretching her ring finger. Her white blood cell (WBC) count and serum C-reactive protein (CRP) level were 12,600/μL and 0.41 mg/dL, respectively. Needle puncture was performed at the orthopedic

[1]Department of Infectious Diseases, Nagoya University Hospital, Japan, [2]Department of Hematology, Japanese Red Cross Nagoya First Hospital, Japan, [3]Department of Virology, Nagoya University Graduate School of Medicine, Japan, [4]Department of Clinical Laboratory, Nagoya University Hospital, Japan, [5]Department of Mycobacteriology, Leprosy Research Center, National Institute of Infectious Diseases, Japan and [6]Department of Hematology, Nagoya University Hospital, Japan
Received: August 31, 2020; Accepted: February 12, 2021; Advance Publication by J-STAGE: March 29, 2021
Correspondence to Dr. Keisuke Oka, koka@med.nagoya-u.ac.jp

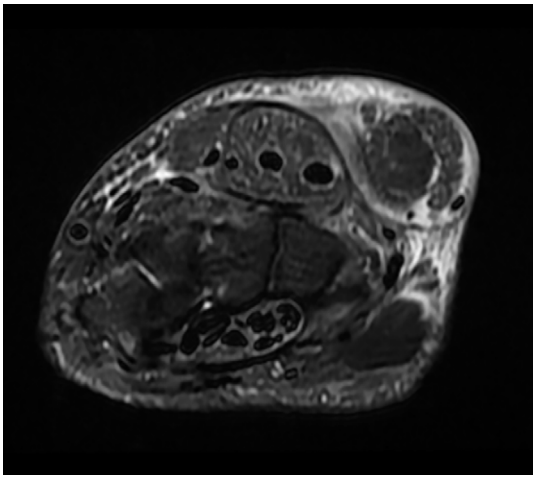

Figure 1. MRI of the right hand in July 20XY. T2 axial fat saturation MRI sequence after the first positive blood culture shows bursitis in the right hand (arrows). MRI: magnetic resonance imaging

Figure 2. Rice bodies obtained from the patient's right hand in August 20XY.

outpatient department. Due to subtle pain and inflammatory response, the treating physician diagnosed her with swollen right opisthenar caused by a benign tumor including the ganglion. No microbiological or pathological tests were performed at this time because of her low platelet levels and high doses of corticosteroids.

Around July 20XY, the mass had gradually enlarged (Fig. 1). In August, incision and drainage of the bursa were performed at the outpatient ward. Acid-fast staining (fluorescence method) of the specimen was positive, but the COBAS TaqMan MAI Test (Roche Diagnostics, Basel, Switzerland) for tuberculosis and MAC yielded negative results. Additional curettage was performed for the mass, and significant rice body formation was removed (Fig. 2). Her general condition was good, and she did not wish to remain hospitalized. Thus, two sets of blood cultures were obtained, and she was discharged.

Mycobacteria isolated from drainage specimens had grown on the Mycobacteria growth indicator tube at day 4 post-curettage. Gram-positive rods grew in the two blood culture samples after 5 days. The DNA-DNA hybridization (DDH) method identified the Mycobacteria isolated from drainage specimens and blood cultures as MABC. The results of antimicrobial susceptibility testing of MABC performed at our hospital are shown in Table a, and the isolate was only susceptible to clarithromycin (CAM). After the diagnosis of bursitis and bacteremia caused by MABC, she agreed to be hospitalized (Fig. 3).

Her physical examination findings on re-admission were as follows: body temperature, 36.3°C; blood pressure, 115/70 mmHg; pulse rate, 103 beats/min; and oxygen saturation, 95% in room air. Her respiratory and cardiac sounds were normal. Her right hand appeared swollen and reddish, and the mass measured 40 mm×40 mm. Laboratory tests results were as follows: elevated serum CRP (2.48 mg/dL), normal WBC count (4,400/μL, neutrophil 70.4%, lymphocyte 17.4%), decreased hemoglobin level (8.4 g/dL), and thrombocytopenia (125,000/μL). Computed tomography (CT) did not reveal disseminated lesions. The patient received combination therapy comprising imipenem/cilastatin, amikacin, and CAM. The local findings of her right hand subsequently improved. After a month, the patient strongly requested to be discharged. Considering her immunosuppressed state and induced CAM resistance due to no other reliable oral regimens based on susceptibility testing, we recommended she continue the same regimens while hospitalized. She was ultimately discharged, and we decided to continue careful follow-up without antibiotic therapy.

In December 20XY, MABC was again detected from blood cultures. Whole-body imaging was repeated, and the following new abnormalities were observed: high signal nodules of the posterior mitral valve, bilateral multiple nodular lung lesions, lumbar disc destruction, and bilateral popliteal cysts. The right popliteal cyst was punctured, but no microbes were detected. We considered the possibility of endocarditis. However, the findings of the valve, an uncommon organism, and clinical course did not lead to a consensus of endocarditis among cardiologists.

Due to the complicated clinical course and shortage of oral antibiotics, we consulted with the National Institute of Infectious Diseases Leprosy Center to identify the subspecies and perform additional antimicrobial susceptibility testing. *M. massiliense* was identified by multiplex polymerase chain reaction (PCR). The results of additional drug susceptibility testing are shown in Table b.

The same antimicrobials were administered to her for eight weeks after confirming negative blood culture. Treatment of recurrent *M. massiliense* bacteremia was switched to the following oral regimen: CAM, sitafloxacin (STFX), and faropenem (FRPM). Based on additional susceptibility results, FRPM was stopped due to the high minimum inhibitory concentration. Two drugs (STFX and CAM) were continued after discharge.

In April 20X(Y+1), she was re-hospitalized for heart fail-

Table. Antimicrobial Susceptibility Testing of *M. Massiliense* Isolated from Blood Culture.

a

	Antimicrobial agent	[a]MIC (μg/mL)		
		20XY/8	20XY/11	20X(Y+1)/4
NUH	Amikacin (AMK)	<8 S	<8 S	<8 S
	Ciprofloxacin (CPFX)	>2 R	>2 R	>2 R
	Clarithromycin (CAM)	<1 S	<1 S	<1 S
	Doxycycline (DOXY)	>1 I or R	>1 I or R	>1 I or R
	Imipenem (IPM)	I	16 I	8 I
	Linezolid (LZD)	8 S	8 S	<2 S
	Moxifloxacin (MFLX)	>4 R	>4 R	2 I
	Trimethoprim/Sulfamethoxazole (TMP/SMX)	>2/38 R	>2/38 R	>2/38 R

b

	Antimicrobial agent	[a]MIC (μg/mL)	
		20XY/8	20XY/11
NIID	Clofazimine (CFZ)	0.03125	0.0625
	Faropenem (FRPM)	128	64
	Sitafloxacin (STFX)	0.5	0.25
	Tedizolide (TZD)	<0.25	<0.25
	Tigecycline (TGC)	0.5	0.5

[a]MICs were determined using broth microdilution methods (CLSI M24-A2).

MIC: minimum inhibitory concentration, CLSI: Clinical and Laboratory Standards Institute, NUH: Nagoya University Hospital, NIID: National Institute of Infectious Diseases

S: susceptible, I: intermediate, R: resistant

(a) Antimicrobial susceptibility testing performed at NUH. (b) Antimicrobial susceptibility testing conducted at NIID. This result was available in February 20X (Y+1).

ure due to worsening AIHA. Two sets of blood culture and one mycobacterial blood culture were collected on admission. Unfortunately, she died two weeks later from gastrointestinal bleeding and respiratory failure. We offered to perform a pathological autopsy, but her family declined. *M. massiliense* was detected from one mycobacterial blood culture bottle after 15 days; antimicrobial susceptibility testing of this isolate is shown in Table a.

Discussion

To our knowledge, this is the first case of bursitis with rice bodies, repeated bacteremia, and disseminated infections caused by *M. massiliense*. At the time of the diagnosis, the patient's chest CT findings were not specific. We therefore suspected that the bursitis had developed after unrecognized trauma of the right hand, which gradually worsened over the next two years. Additionally, long-term corticosteroids use for ITP and AIHA likely triggered bacteremia and disseminated lesions in this case.

MABC is considered the most pathogenic RGM to mainly cause respiratory infections. A retrospective cohort study of 108 MABC infections showed the following types: 59 (54.6%) respiratory infections, 21 (19.4%) bloodstream infections (BSIs), 10 (9.2%) skin and soft tissue infections, and 3 (2.8%) disseminated infections (4). Regarding disseminated MABC infections, the duration from the symptom onset to the diagnosis was over 3 months in 48% of cases (5). The mortality rate of patients with disseminated infections is relatively high, especially among immunosuppressed patients (5).

While the exact pathophysiology of rice body formation remains unclear, rice bodies are thought to form as the result of nonspecific responses to chronic synovial inflammation. Metaplasia of subsynovial connective tissue into cartilage nodules is observed. Rice bodies are associated with tuberculous arthritis, osteoarthritis and infective arthritis, and rheumatoid arthritis (6). Bursitis caused by NTM is thought to be a very rare presentation (7-9); thus, the optimal duration of antimicrobial therapy for bursitis caused by NTM is unclear. Long-term antimicrobial therapy is generally performed (8). Furthermore, the optimal duration of antimicrobial therapy for bursitis with rice bodies caused by MABC remains unknown.

Subspecies identification of MABC is recommended by the American Thoracic Society/the Infectious Diseases Society of America guideline (10). Subspecies identification helps infer antimicrobial susceptibility. For example, *M. abscessus* and *M. bolletii* have an activated *erm* gene and resistance to macrolide drugs, whereas *M. massiliense* is usually susceptible to CAM (11). DDH and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, which are usually performed in Japan, cannot distinguish MABC subspecies (12, 13). MABC is reportedly resistant to all standard anti-tuberculous drugs; thus, no reliable treatment regimen exists. It is important to select antimicrobials

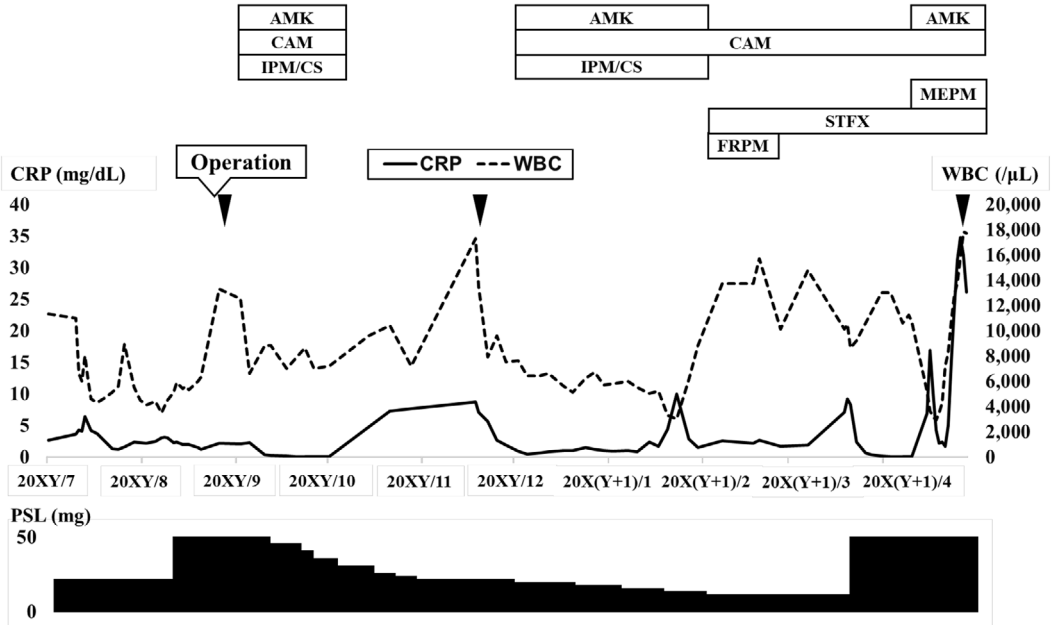

Figure 3. **Clinical course of the present case. Arrowheads indicate time points at which positive blood cultures were obtained. Solid line indicates the CRP level, dotted line indicates the WBC count. AMK: amikacin, CAM: clarithromycin, CRP: C-reactive protein, FRPM: faropenem, IPM/CS: imipenem/cilastatin, PSL: prednisolone, MEPM: meropenem, STFX: sitafloxacin, WBC: white blood cell**

based on appropriate susceptibility testing. However, appropriate susceptibility testing for candidate agents, such as STFX and FRPM, is difficult to perform in Japanese general hospitals. We therefore suspect that most clinicians are not confident about how best to treat disseminated MABC infections. In the present case, subspecies identification by multiplex PCR and additional antimicrobial susceptibility testing led us to select an oral regimen comprising STFX and CAM.

Two points need to be discussed in this case: the delayed diagnosis and optimal antimicrobial therapy. First, the patient's presentation with a swollen joint without pain and redness and subtle inflammatory response led to a misdiagnosis of non-infective bursitis for two years. A delayed diagnosis of bursitis caused by NTM has been previously reported (8). We considered that the delayed diagnosis of bursitis caused by *M. massiliense* in the present case resulted in rice body formation and *M. massiliense* BSI. Therefore, clinicians must consider infective bursitis caused by NTM in immunocompromised patients, even if they do not complain of pain or have subtle pain in swollen joints. Blood cultures may contribute to the early diagnosis of disseminated RGM infections when clinicians encounter immunosuppressed patients with chronic bursitis. Second, long-term antimicrobial therapy is needed and should be initiated at the diagnosis. However, we were unable to determine an effective combination regimen based on antimicrobial susceptibility testing at our hospital. Early consultation with a specific center about species identification and antimicrobial susceptibility testing for MABC isolate might help improve the prognosis of patients with disseminated MABC infections who require long-term therapy. BrothMIC RGM® (Kyokuto Pharmaceutical Industrial, Tokyo, Japan) has been available in Japan since 2019 (14), so we have been able to obtain susceptibility results of RGM based on the Clinical and Laboratory Standards Institute in community hospitals. While further evaluations are necessary for some antimicrobials on the panel, BrothMIC RGM® is expected to be useful for determining effective regimens for RGM infections.

In conclusion, the early diagnosis of disseminated MABC infection is essential, and the ideal treatment regimen and duration of treatment for severe MABC infections should be determined based on precise species identification and antimicrobial susceptibility testing. The accumulation of more cases is necessary to determine the optimal management of disseminated MABC infection.

Author's disclosure of potential Conflicts of Interest (COI).
Hitoshi Kiyoi: Honoraria, Bristol-Myers Squibb, Astellas Pharma and Novartis; Research funding, Fujifilm and Daiichi Sankyo. Tetsuya Yagi: Honoraria, MSD.

Financial Support

This work was supported in part by grants from the Japan Agency for Medical Research and Development/Japan International Cooperation Agency (AMED) to Y. Hoshino (grant nos. jp 20fk0108064, jp20fk0108075, jp20fk0108093, jp20fk0108129, jp 20jm0510004, jp20wm0125007, jp20wm0225004, and jp20wm 0325003), Grant-in-Aids for Scientific Research (B) and (C) to Y. Hoshino (grant nos. jp20H02282 and jp18K08312), grants for Early-Career Scientists to H. Fukano (grant no. jp18K15966) and a grant for Fostering Joint International Research (B) to Y.

Hoshino (grant no. jp19KK0217) from the Japan Society for the Promotion of Science (JSPS). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Morimoto K, Hasegawa N, Izumi K, et al. A laboratory-based analysis of nontuberculous mycobacterial lung disease in Japan from 2012 to 2013. Ann Am Thorac Soc **14**: 49-56, 2017.
2. Furuuchi K, Morimoto K, Yoshiyama T, et al. Interrelational changes in the epidemiology and clinical features of nontuberculous mycobacterial pulmonary disease and tuberculosis in a referral hospital in Japan. Respir Med **152**: 74-80, 2019.
3. Tanaka E. Treatment and prognosis of infections with rapidly growing organisms. Kekkaku **88**: 757-761, 2013.
4. Sfeir M, Walsh M, Rosa R, et al. Mycobacterium abscessus complex infections: a retrospective cohort study. Open Forum Infect Dis **5**: ofx259, 2018.
5. Fukui S, Sekiya N, Takizawa Y, et al. Disseminated *Mycobacterium abscessus* infection following septic arthritis: a case report and review of the literature. Medicine (Baltimore) **94**: e861, 2015.
6. Bacha R, Manzoor I, Gilani SA. Sonographic presentation of rice bodies in subacromial-subdeltoid chronic bursitis. Ultrasound J **11**: 16, 2019.
7. Rutten MJ, van den Berg JC, van den Hoogen FH, et al. Nontuberculous mycobacterial bursitis and arthritis of the shoulder. Skeletal Radiol **27**: 33-35, 1998.
8. Working S, Tyser A, Levy D. Mycobacterium avium complex olecranon bursitis resolves without antimicrobials or surgical intervention: a case report and review of the literature. IDCases **2**: 59-62, 2015.
9. Garrigues GE, Aldridge JM 3rd, Toth AP, Stout JE. Nontuberculous mycobacterial olecranon bursitis: case reports and literature review. J Shoulder Elbow Surg **18**: e1-5, 2009.
10. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med **175**: 367-416, 2007.
11. Morimoto K, Nakagawa T, Asami T, 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**: 14-20, 2018.
12. Saleeb PG, Drake SK, Murray PR, Zelazny AM. Identification of mycobacteria in solid-culture media by matrix-assisted laser desorption ionization-time of flight mass spectrometry. J Clin Microbiol **49**: 1790-1794, 2011.
13. Kusunoki S, Ezaki T, Tamesada M, et al. Application of colorimetric microdilution plate hybridization for rapid genetic identification of 22 *Mycobacterium* species. J Clin Microbiol **29**: 1596-1603, 1991.
14. BrothMIC RGM, Kyokuto Pharmaceutical Industrial CO., LTD (in Japanese) [Internet]. [cited 2021 Jan 26]. Available from: https://ssl.kyokutoseiyaku.co.jp/upload/item/351162-1.pdf