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Arthroscopic treatment of *Mycobacterium massiliense* septic arthritis outbreak after intra-articular injection

A case-series report and literature review

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Abstract

Non-tuberculous mycobacteria (NTM) comprise mycobacteria, with the exceptions of *Mycobacterium (M.) leprae* and the *M. tuberculosis* complex. Septic arthritis caused by NTM is so rare that there is no standardized treatment.

Between April and September 2012, 27 patients were infected with *M. massiliense* in a single clinic following injection of steroid in the knee joint. Clinical data of 9 patients who received arthroscopic treatment in Seoul Hospital of Soonchunhyang University were analyzed retrospectively.

Arthroscopic irrigation and debridement were performed average 2.6 times (1–3 times). As 6 out of 9 cases (67%) had joint contracture of the knee joint, arthroscopic adhesiolysis, and brisement were performed. After surgical procedures, Hospital for Special Surgery and Lysholm knee score showed improvement compared before the surgery, but a radiographic result evaluated by Kellgren-Lawrence revealed that 6 cases got deteriorated to stage 4 in the 4-year follow-up.

NTM septic arthritis had a higher recurrence and a higher contracture incidence than septic arthritis caused by tuberculous mycobacteria or other bacteria. Treatment was possible with repeated arthroscopic debridement and intravenous antibiotics.

Abbreviations: HSS = hospital for special surgery, K-L = Kellgren-Lawrence, M. = *Mycobacterium*, NTM = Non-tuberculous mycobacteria.

Keywords: arthroscopy, intra-articular injection, *Mycobacterium massiliense*, septic arthritis

1. Introduction

Non-tuberculous mycobacteria (NTM) comprise mycobacteria, with the exceptions of *Mycobacterium (M.) leprae* and the *M. tuberculosis* complex. To date, 150 different species have been recognized, with new species continuously being reported.[1] NTM are found throughout nature in soil, water, dust, and livestock. Most species cause lung disease and some cause lymphadenitis, dermatosis, or musculoskeletal disease. Musculoskeletal infections have rarely been reported. They are caused by injection treatment and surgical procedures.[2,3] A skin tissue infection caused by the intramuscular injection of *M. massiliense* has been described, but joint infection has not been reported yet.

In 2012, the Korean Institute of Drug Safety reported the infection of 27 patients by *M. massiliense* in a single primary care clinic. All patients had received an injection around and in a joint.[4] Among them, 9 patients were treated in our hospital, and their clinical patterns and use of antibiotics were reported.[5] For septic arthritis, it is important to perform a combination therapy involving antibiotics and surgical treatment. Selection of the appropriate antibiotics based on the isolated microorganism is also crucial. However, septic arthritis caused by NTM is so rare that there is no standardized treatment, and no literature can be found regarding joint infection by *M. massiliense*.

To provide some clarity, we report our experience on the surgical treatment of the 9 aforementioned patients for the NTM-related septic arthritis, their clinical patterns, and the result of a 4-year follow-up.

2. Patients and methods

Twenty-seven patients became infected by *M. massiliense* following injection of steroid and drugs including local anesthetic (triamcinolone +saline + lidocaine) into the soft tissue around and in the knee joint from April to September 2012 in a single primary care clinic. Of the 27, 9 cases treated in our hospital. We retrieved

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the medical records of 9 patients through chart review and performed a retrospective observational study of a 4-year follow-up. Culture results, types and duration of antibiotics used, a number of arthroscopic treatments, range of motion, Hospital for Special Surgery (HSS) knee score, Lysholm knee score, contracture occurrence, and final Kellgren-Lawrence (K-L) grade were analyzed.

Under Korean law, this type of study, which relies on a retrospective analysis of the past patient records, does not need the approval of the institutional review board. All patients have provided written informed consent for publication of the cases.

3. Results

3.1. General information

The 9 patients comprised 1 male and 8 females with an average age at the time of the first hospital visit of 58.8 years (range, 49–71 years). The mean follow-up period was 57 months (range, 48–71 months). Underlying internal diseases included hypertension (n=2), diabetes (n=3), breast cancer (n=1), hypothyroidism (n=1), hyperlipidemia (n=1), and psoriasis (n=1). Septic arthritis was present in both knee joints (n=7), right knee (n=1), and left knee (n=1). Abscess in addition to the joint area occurred in the neck (n=1), lumbodorsal fascia (n=4), hip joint (n=4), femoral (n=3), and on the leg (n=3). The average time to develop septic arthritis after injection was 4.7 weeks (range, 2–9 weeks). The number of injection treatments in the single primary care clinic was 2 (n=2), 4 (n=1), 5 (n=1), 6 (n=2), more than 6 (n=1), more than 8 (n=1), and more than 10 (n=1). Among these, 3 patients did not remember the exact number of injections they received. When they came to our hospital, all 9 patients had symptoms of septic arthritis that included pain, edema, and fever. Among them, 8 had the fever all over their bodies, and 6 had limited mobility of knee joint

3.2. Diagnostic tests

We investigated the examination findings of each patient's peripheral blood and synovial tests, and the result of microbiologic analysis performed at the time of arrival to our hospital. We also investigated the type of prescribed antibiotics and the duration of antibiotic use, the type and number of procedures, and arthroscopic findings. A biopsy was performed on the synovia obtained through arthrocentesis and the necrotic joint tissue obtained through arthroscopy and biopsy. Gram chromatin, acid-fast bacilli (AFB) chromatin, bacterial identification, and AFB culture were also performed. Polymerase chain reaction (PCR) for the TM and NTM as well as PCR-restriction fragment length polymorphism (PCR-RFLP) analysis was performed for identification of fungi from the tissues of all patients.

3.3. Surgical treatment and postoperative management

Arthroscopy performed for septic arthritis of the knee joint used general or spinal anesthesia. The arthroscopy was inserted into the anteromedial, anterolateral, superolateral or, if necessary, the posteromedial portal. Synovial material was obtained for culture testing. Biopsied material was washed using normal saline while being closely observed through the arthroscopy, and necrotic tissue and floaters were removed. Rather than removing all the synovial material, we only removed the areas affected by necrosis or severe inflammation. Arthroscopy revealed stage III on Gächter Criteria for all 9 patients (Table 1).

After the arthroscopic operation, a hemovac was inserted for drainage. When the effusion was clear to the naked eye and the amount of the drainage was less than 50 cc, the hemovac was removed. After the arthroscopic operation, edema and pain were exacerbated due to the increase of effusion. When the level of C-reactive protein (CRP) increased on the hemodynamic follow-up test, arthroscopy was performed again. Patients wore a splint until the hemovac was removed after the operation. For the first week after the removal of the splint, patients performed passive exercise and then proceeded to active joint exercise. In the case of joint contracture in which the range of active or passive joint motion did not increase more than 90 degrees, arthroscopic adhesiolysis and bridement procedures were performed. HSS knee score, Lysholm knee score, and joint range of motion were measured before the operation and at the end of the 4-year follow-up. Radiological assessment was conducted before the operation and at the end of the follow-up using the K-L grading system.

3.4. Laboratory follow-up and antibiotics treatment

The peripheral blood test done at the time of first visit revealed increased erythrocyte sedimentation ratio (ESR) in all 9 cases (33–120 mm/hr). CRP increased in 8 cases (0.94–27.42 mg/dL) with the remaining patients displaying CRP level of 0.17 mg/dL). In the synovial test using knee joint arthrocentesis, the leukocyte count increased in all 9 cases (leukocyte count 1368–53280/μL;

Table 1

Laboratory findings of 9 cases.

	Peripheral blood analysis				Synovial fluid analysis				
Case	WBC(/μℓ) (4.0–10.0)	Neutrophil(%) (40–74)	ESR(mm/hr) (0–20)	CRP(mg/dL) (0.0–0.5)	WBC(/μℓ) (<200)	Neutrophil(%) (<25)	AFB	PCR MTB/NTM	PCR-RFLP
1	11100	81.5	33	0.17	17280	40	+	+	*M. massiliense*
2	7200	79.4	120	8.53	11232	69	+	+	*M. massiliense*
3	7500	66.0	63	2.49	11520	41	+	–	*M. massiliense*
4	6300	91.2	120	9.87	3780	10	+	+	*M. massiliense*
5	9300	76.6	120	4.84	44280	33	+	+	*M. massiliense*
6	8600	72.2	88	13.15	4770	81	+	+	*M. massiliense*
7	10900	75.8	33	0.84	1368	44	–	–	-
8	9600	78.8	100	18.92	28800	95	+	–	*M. massiliense*
9	13500	81.3	120	27.42	53280	90	+	+	*M. massiliense*

– = negative, + = positive, AFB = acid fast bacillus, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PCR MTB/NTM = polymerase chain reaction *Mycobacterium tuberculosis*/nontuberculous mycobacteria, RFLP = restriction fragment length polymorphism, WBC = white blood cell.

Table 2

Summary of 9 cases (clinical characteristic and treatment).

Case	Sex/ age	Underlying disease	Duration of symptoms (wk)	Affected site	Injection count	Surgery	Antibiotic combination therapy (d, In order of administration)
1	F/52	HTN	4	Both knee, back, buttock, Lt. thigh, Lt. calf	6	Rt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x3) Lt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x3) Back: I&D(x3) Buttock, Lt. thigh, Lt. leg: I&D(x1)	Cefazolin (2) Ceftazidime + Vancomycin (7) Imipenem + Clarythromycin + Amikacin (171) Amikacin stop (stopped in 30 d, S/E: dizziness) Imipenem stop (stopped in 110 d)
2	F/54	Breast cancer	4	Both knee	6	Rt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x1) Lt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x1)	Cefazolin (2) Ceftazidime + Vancomycin (3) Imipenem + Clarithromycin + Amikacin (184) Vancomycin add (d/t MRCNS: Sta. hominis) Vancomycin (5) change to Teicoplanin (17) (d/t vancomycin low level) Amikacin stop (stopped in 68 d) Imipenem stop (stopped in 81 d)
3	F/57	DM	6	Both knee, back	2	Rt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x1) Lt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x1) Back: I&D(x1)	Cefazolin (4) Vancomycin + Ceftazidime (3) Amikacin + Imipenem + Clarithromycin (174) Amikacin stop (stopped in 34 d) Imipenem stop (stopped in 80 d)
4	F/71	HTN, DM	3	Both knee, Rt. calf back, buttock, neck	>6	Rt. knee A/S irrigation and debridement(x3) Lt. knee A/S irrigation and debridement(x3) Back, Neck: I&D(x5) Buttock, Lt. leg: I&D(x3)	Cefazolin (1) Cefazidime + Vancomycin (3) Cefazidime + Teicoplanin (2) Amikacin (16) + Imipenem (71) + Clarithromycin (117) Imipenem (34) + Clarithromycin (98) Imipenem (15) + Clarithromycin (62) Imipenem (25) + Clarithromycin (29) Clarithromycin (77) + linezolid (57) Amikacin (20) + Imipenem (20) + Clarithromycin (294) Clarithromycin (99)
5	F/59	Hypothyroidism	3	Lt. knee, buttock, Lt. calf	4	Lt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x1) Buttock, Lt. leg: I&D(x1)	Cefazolin (1) Vancomycin + Ceftazidime (3) Amikacin + Imipenem + Clarithromycin (100) Amikacin stop (stopped in 27 d) Imipenem stop (stopped in 81 d) Imipenem + Clarithromycin (160) Imipenem stop (stopped in 25 d)
6	F/65	DM	7	Lt knee, back, Lt. thigh	>8	Lt. knee A/S irrigation and debridement(x2) Back, Lt. thigh: I&D(x1)	Vancomycin + Ceftazidime (2) Imipenem + Clarithromycin (399) Amikacin add (3 d later) Amikacin stop (stopped in 29 d) Imipenem stop (stopped in 81 d)
7	F/64	Hyperlipidemia	2	Rt. knee	5	Rt. knee A/S irrigation and debridement(x1)	Vancomycin + Ceftazidime (3) Amikacin + Imipenem + Clarithromycin (321) Amikacin stop (stopped in 29 d) Imipenem stop (stopped in 46 d)
8	F/49	-	5	Both knee	>10	Rt. knee A/S irrigation and debridement(x2) A/S adhesiolysis and bricement(x1) Lt. knee	Amikacin + Imipenem + Clarithromycin (67) Amikacin stop (stopped in 6 d)

(*continued*)

Table 2

(continued).

Case	Sex/ age	Underlying disease	Duration of symptoms (wk)	Affected site	Injection count	Surgery	Antibiotic combination therapy (d, In order of administration)
						A/S irrigation and debridement(x2) A/S adhesiolysis and bricement(x1)	Cefoxitin + Clarithromycin (164) Cefoxitin stop (stopped in 48 d) Clarithromycin + Linezolid (88) Linezolid stop (stopped in 14 d) Cefoxitin + Amikacin + Clarithromycin (182) Cefoxitin and Amikacin stop (stopped in 13 d)
9	M/61	Psoriasis	5	Both knee, Lt. thigh Lt. buttock	2	Rt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x2) Lt. knee A/S irrigation and debridement(x3) A/S adhesiolysis and bricement(x2) buttock, Lt. thigh: I&D(x3)	Vancomycin + Ceftazidime (1) Amikacin + Imipenem + Clarithromycin (253) Amikacin stop (stopped in 27 d) Imipenem (stopped in 233 d)

A/S = arthroscopic, DM = diabetes mellitus, HTN = hypertension, Lt = left, MRCNS = methicillin-resistant coagulase-negative staphylococci, Rt = right, S/E = side effect, Sta. = Staphylococcus.

normal range:4.0–10.0/μL) as did the polymorphonuclear leukocyte ratio (33–91.2%; normal range, 40–74%). The average duration for the normalization of CRP was 16 weeks (range, 2–30 weeks) after the operation. In 1 case, CRP normalized 2 weeks after the first operation, but the CRP level in that patients rose and the symptoms were exacerbated, prompting reoperation. Eight weeks later CRP had normalized. In the remaining 7 cases, despite administering the appropriate antibiotics after determining antibiotic sensitivity of the infecting *M. massiliense* and performing an arthroscopy, CRP normalization was achieved after 8 to 30 weeks.

Culture testing using MTB/NTM PCR revealed the average duration of positive findings in 6 cases was 7.8 days (range, 7–9 days) after obtaining the specimen. AFB culture testing found that the average duration of a positive finding in 8 cases was 51 days (range, 35–67 days) after the operation. PCR-RFLP testing performed at The Korean National Tuberculosis Association identified *M. massiliense* in 8 cases. The remaining cases presented negative findings on the AFB culture and MTB/NTM PCR tests (Table 2).

Antibiotic treatment was adjusted according to the culture results and clinical features of the patient in consultation with an infection specialist. In most cases, combination therapy of antibiotics was required. All 9 patients received Clarithromycin (174–776 days), Amikacin (16–68 days), and Imipenem (46–233 days). The first generation cephalosporin, Cefazolin was used in 6 cases as a prophylactic antibiotic monotherapy before and after surgery. (1–4 days). Third generation cephalosporin such as Ceftazidime were combined with vancomycin in 7 cases (2–7 days). Teicoplanin and Linezolid were applied in combination therapy with other antibiotics in 2 cases, respectively (Table 3).

3.5. Specific findings and clinical outcomes

Surgical procedures were performed on each patient an average of 6.3 times (range, 1–14). Under the diagnosis of the septic arthritis of the knee joint, arthroscopic irrigation, and debridement was done an average of 2.6 times (range, 1–3). Joint contracture of the knee occurred in 6 of 9 cases, which prompted arthroscopic adhesiolysis and manipulation. Also, in 7 cases, apart from the septic arthritis of the knee joint, abscess occurred in other regions as previously.

Arthroscopic findings were similar in all 9 cases. With the floater in the joint, thickened and hyperemic Synovial membrane and partial necrotic findings were observed. Degeneration and necrosis findings around the fat in the joint and the fat pad were also observed (Fig. 1). Even after performing arthroscopic irrigation and debridement, septic effusion lasted for a long time, and in some case, the abscess was drained through the portal of the arthroscopy (Fig. 2).

After performing arthroscopic debridement on the area with degeneration and necrosis of the fat pad and hypodermic fat, skin dimpling was observed, which occurred due to the lack of hypodermic fat in the area where the arthroscopy was inserted (Fig. 3). The abscess in the area around the injection apart from the joints was encapsulated, which had the pattern of abscess forming in the capsule. However, in 1 case with an abscess

Table 3

Septic arthritis of the knee stage according to the Gächter criteria.

Stage	Arthroscopic findings	Radiologic findings
I	Opacity of fluid, redness of the synovial membrane, and possible petechial bleeding	No finding
II	Severe inflammation, fibrinous deposition, and pus	No finding
III	Thickening of the synovial membrane, compartment formation, and sponge like, especially in the suprapatellar pouch	No finding
IV	Aggressive pannus with infiltration of the cartilage, possibly undermining the cartilage	Subchondral osteolysis, possible osseous erosions, and cysts

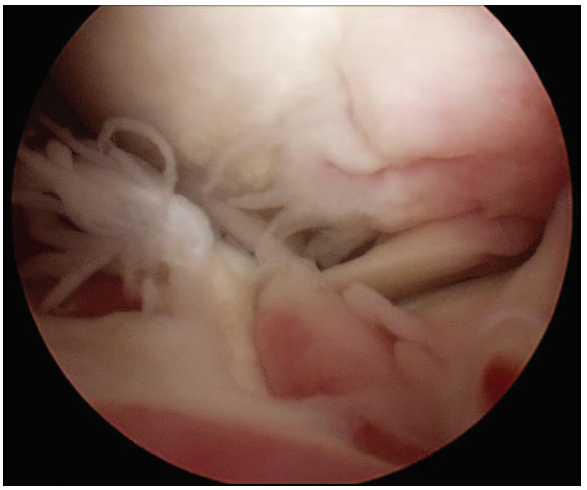

Figure 1. Arthroscopic findings in case of septic arthritis of knee joint.

around the lumbodorsal, multiple abscesses occurred in the area where the injection had not been given, and encapsulation was not observed (Fig. 4).

Microscopic examination of the necrotic synovial fluid obtained at the time of the arthroscopic operation revealed many necrotizing or non-necrotizing granuloma. The granuloma were multi-nuclear giant cells and lymphocytes including epithelial macrophage, and Langhans' giant cells (Fig. 5).

HSS knee score averaged 18.9 (range, 2–37) before the operation and 72.82 (range, 58–88) at the 4-year follow-up. Lysholm knee score averaged 17.2 (range, 0–35) before the operation and 66.3 (range, 33–85) at the 4-year follow-up. The joint range of motion was normal for 6 of the 9 cases at the final follow-up (Table 4). Six cases had exacerbated to stage IV in the radiological assessment and 3 cases were normal in K-L stage change (Table 5).

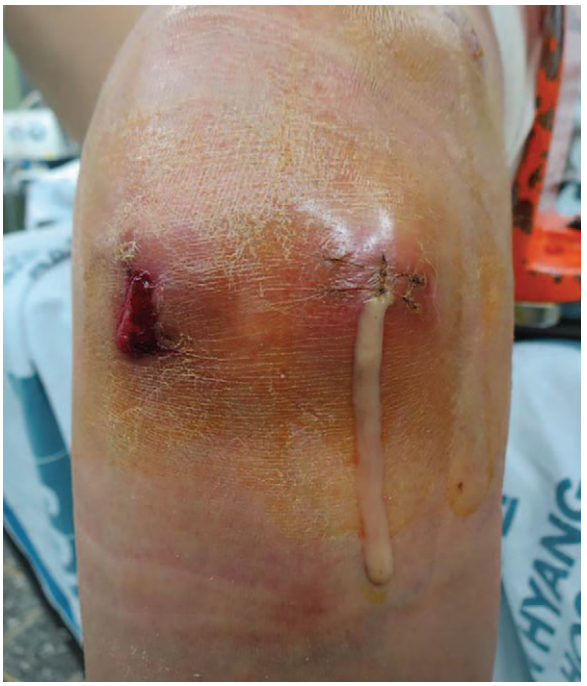

Figure 2. Recurred purulent discharge after arthroscopic debridement.

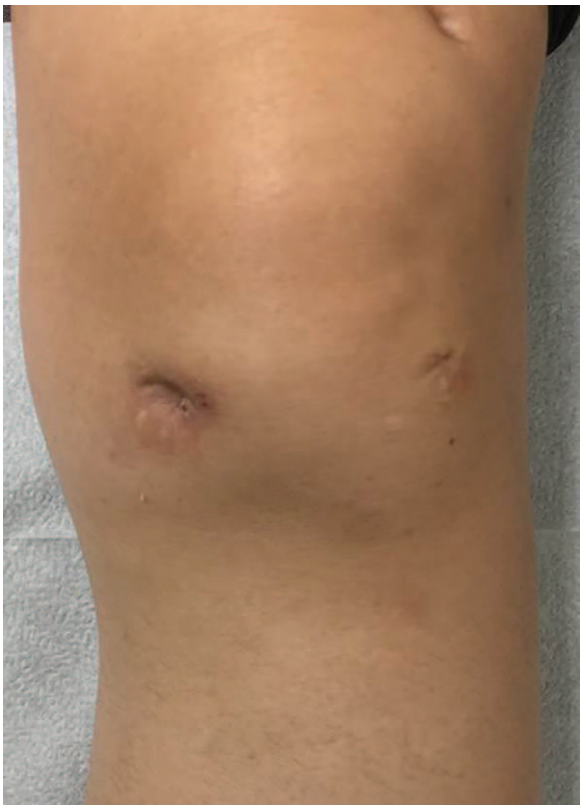

Figure 3. Skin dimpling after arthroscopic operation.

4. Discussion

The recent increased incidence of NTM infections is thought to be related to the increased medical procedures like injection treatment and surgery, increased use of antibiotics, and advanced technology to identify mycobacteria.[6] Rapid Growing *M.* (RGM), as the name implies, display rapid growth and can be identified by gross examination within 7 days on solid medium.

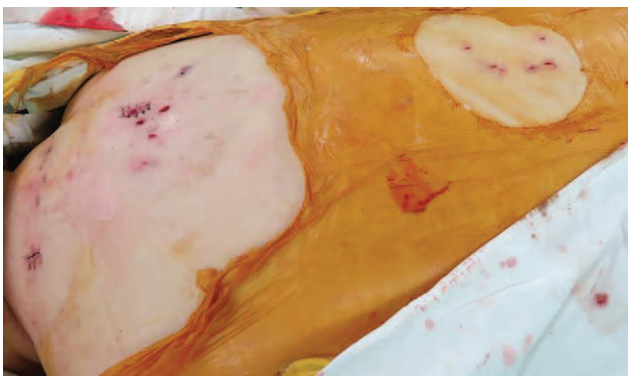

Figure 4. Multiple incision and drainage wound for multiple abscess in the back.

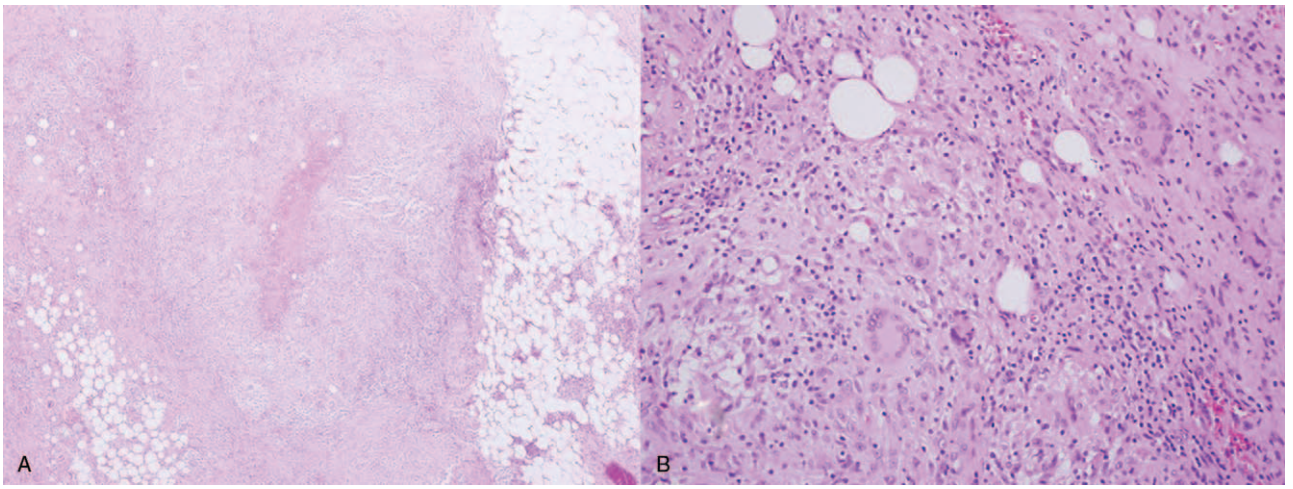

Figure 5. Synovial tissue of the knee joint shows chronic granulomatous lesion with central caseous necrosis in fibroadiopose tissue(A). These granulomatous lesions are composed of the epithelioid histiocytes, multinucleated giant cells including Langhans' giant cells, and the lymphocytes(B).

RGM includes *M. chelonae*, *M. abscessus*, and *M. immunogenum*. *M. abscessus* is sub-divided into *M. abscessus* sensu stricto, *M. massiliense*, and *M. bolletii*.[7] *M. massiliense* is separated from the *M. abscessus* group as the former possesses an erythromycin ribosomal methylase (ERM) gene. *M. abscessus* displays a general resistance to macrolide antibiotics due to the partial genetic defect. In contrast, *M. massiliense* has been reported to have a good treatment response to combined therapy including clarithromycin.[8] *M. massiliense* isolates had a sensitivity to fluoroquinolone antibiotics of about 50% in 1 study.[9] Another study reported that a combined antibiotic therapy using fluoroquinolone and clarithromycin together was effective in treating *M. massiliense* lung disease.[10] However, in our study, 6 of the 9 cases were resistant to fluoroquinolone antibiotics.

We used a first-generation cephalosporin for 6 cases when they first visited our hospital based on our experience. However, as the possibility of a collective infection after injection treatment in a single clinic grew, we changed the antibiotic therapy to the third-generation antibiotics Vancomycin and Ceftazidime. These are typically used to treat infections by methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Vancomycin and Ceftazidime were used for 2 cases who visited our hospital a few days later. While receiving Vancomycin, 2 of 8 cases developed an adverse drug reaction, so therapy was changed to Teicoplanin (2 days). As the earlier 6 cases had the positive findings on the MTB/NTM PCR test, we changed their antibiotics to the combination of oral Clarithromycin and Amikacin, and Imipenem by injection for the treatment of NTM. Finally, in 6 of the 9 cases, *M. massiliense* was identified by PCR-RFLP and were shown on antibiotic sensitivity testing to be sensitive to Clarithromycin, Amikacin, and Imipenem that were being used. In 2 cases, *M. massiliense* was identified by PCR-RFLP, but antibiotic sensitivity tests were not analyzed. One case had a negative finding concerning fungus identification and antibiotics sensitivity test results were not analyzed. The patients had received an injection at the same hospital at the same time and experienced the same time of onset and a similar clinical pattern. Therefore, the patient was treated assuming the presence of

Table 4

Functional result of 9 cases.

	HSS score		Lysholm score		
Case	**Pre-op**	**Post-op 4 yr**	**Pre-op**	**Post-op 4 yr**	**Post-op 4 yr ROM**
1	Rt: 16	Rt: 66	Rt: 2	Rt: 48	Rt: Full
	Lt: 16	Lt: 76	Lt: 2	Lt: 53	Lt: Full
2	Rt: 2	Rt: 58	Rt: 0	Rt: 33	Rt: 120
	Lt: 2	Lt: 58	Lt: 0	Lt: 33	Lt: 110
3	Rt: 30	Rt: 79	Rt: 35	Rt: 75	Rt: 120
	Lt: 30	Lt: 88	Lt: 35	Lt: 85	Lt: Full
4	Rt: 14	Rt: 81	Rt: 13	Rt: 80	Rt: Full
	Lt: 14	Lt: 81	Lt: 13	Lt: 80	Lt: Full
5	Lt: 12	Lt: 60	Lt: 8	Lt: 80	Lt: Full
6	Lt: 18	Lt: 74	Lt: 19	Lt: 79	Lt: Full
7	Rt: 16	Rt: 66	Rt: 18	Rt: 43	Rt: 125
8	Rt: 37	Rt: 84	Rt: 30	Rt: 70	Rt: Full
	Lt: 37	Lt: 84	Lt: 30	Lt: 70	Lt: Full
9	Rt: 25	Rt: 77	Rt: 30	Rt: 82	Rt: Full
	Lt: 25	Lt: 77	Lt: 30	Lt: 82	Lt: Full

HSS = Hospital for Special Surgery, Lt = left, op = operation, ROM = range of motion, Rt = right.

Table 5

Arthroscopic and radiologic stage of 9 cases.

Case	Gächter stage	K-L stage	
		Pre-op	Post-op 4 yr
1	Rt: 3	Rt: 0	Rt: IV
	Lt: 3	Lt: 0	Lt: IV
2	Rt: 3	Rt: 0	Rt: IV
	Lt: 3	Lt: 0	Lt: IV
3	Rt: 3	Rt: III	Rt: IV
	Lt: 3	Lt: I	Lt: IV
4	Rt: 3	Rt: I	Rt: IV
	Lt: 3	Lt: I	Lt: IV
5	Lt: 3	Lt: 0	Lt: 0
6	Lt: 3	Lt: 0	Lt: IV
7	Rt: 3	Rt: III	Rt: IV
8	Rt: 3	Rt: 0	Rt: 0
	Lt: 3	Lt: 0	Lt: 0
9	Rt: 3	Rt: 0	Rt: I
	Lt: 3	Lt: 0	Lt: I

K-L = Kellgren-Lawrence, Lt = left, op = operation, Rt = right.

M. massiliense infection. During the antibiotic treatment, complications occurred. Hearing impairment in 4 cases and acute kidney disease in 1 case prompted the cessation of Amikacin (6–68 days). For 2 cases who displayed sensitivity to Clarithromycin, Amikacin, and Imipenem and for whom *M. massiliense* was identified, linezolid was administered additionally for a sufficient period of time (14–57 days) since the abscess on the soft tissue occurred additionally without improvement of symptoms, even though the antibiotics were used for a long time. Excluding Cefazolin, Vancomycin, and Ceftazidime, the average duration of the antibiotic therapy was 382.9 days (range, 174–776 days).

In the treatment of *M. massiliense* infection, standards for the principle, type, and duration of antibiotic therapy have not been established. A combination therapy using amikacin, cefoxitin, and doxycycline for 6 months was reportedly effective in treating *M. massiliense* skin infection,[11] while another study reported that a single therapy using clarithromycin for 6 months was effective in treating a *M. massiliense* skin infection resistant to fluoroquinolone.[12] Therefore, it is considered reasonable to select antibiotics after antibiotics sensitivity testing.

The duration of antibiotics of 12 to 19 months has been recommended for NTM deep infections.[13] NTM hand and wrist infections were reported to be completely cured using antibiotics for 5 to 34 months; since 2 cases who stopped taking antibiotics arbitrarily were also cured completely, the authors concluded that it is difficult to establish the standards for the duration of the antibiotic therapy.[14]

Most of the reports concerning NTM have been related to lung infections or soft tissue infections due to *M. massiliense*. While 2 cases of NTM infection in the knee joint were reported in 1979,[15] they were infections due to *M. chelonei*. Musculoskeletal infections by *M. massiliense* after having an intramuscular injection and cosmetic surgery have been reported,[3,16] as was an infection around a pacemaker.[9] But, joint infection by *M. massiliense* has not been reported until now.

Diagnosing NTM at the early stage of infection is not easy.[13] The disease has a low virulence. Patients may go to hospital late because the clinical symptoms can go unnoticed due to its slow development, or the patients may undergo self-treatment using an anti-inflammatory agent. Second, there is little clinical experience with NTM diseases. Lastly, without a *M.* culture, the experiential antibiotics are being extensively used based on sensitivity results from other bacteria.

In 1 study, the diagnosis of osteomyelitis by *M. chelonei* was delayed at most 8 months.[17] Another study reported that it took 2 months to diagnose a case of foot osteomyelitis after identifying *M. abscessus*.[18] Therefore, to diagnose NTM infection in the musculoskeletal patients, it is necessary to include tests for NTM as well as bacteria, fungus, and TM.

On the synovial test through an arthrocentesis, the leukocyte count and the ratio of polymorphonuclear leukocyte were elevated in all 9 cases, but the number did not meet the inclusion criteria of septic arthritis by the bacterial infection (>50000/μL leukocytes, > 90% of polymorphonuclear leukocytes). For septic arthritis, early diagnosis and treatment are crucial to determine the prognosis. If the surgical debridement fails, it can develop complication such as osteomyelitis, osteonecrosis, ankylosis, or secondary arthritis.[19,20] Arthroscopy may be more effective than conventional gonarthrotomy.[21,22]

Arthroscopic irrigation can have an effect on preventing joint cartilage from being destroyed by decreasing the pressure in the joint and removing the necrotic tissue. Currently, the standard principle of the septic arthritis is to use combination therapy with generalized antibiotics, arthroscopic decompression, and repeated arthroscopic irrigation.[23] When treating patients with Gächter stage 3 with arthroscopy, we recommend removing the necrotic tissue and tissue adhesive using a shaver. Some studies recommended not removing the synovial membrane at the beginning of the operation, since this membrane play protects from the infiltration of microbes.[24–26] Although some studies suggested removing the synovial membrane at the beginning of treatment to prevent reinfection from any indolent infection,[21,27] the cases cited involved infection by bacteria and not by NTM. No studies have reported cases of infection by NTM and *M. massiliense*. All the 9 cases included in this study were Gächter stage 3, and only the area showing severe inflammatory change in the synovial membrane was removed. The average number of arthroscopic irrigations and debridements for knee joint infection was 2.6 (range, 1–3). As 6 of 9 cases (67%) developed joint contracture, arthroscopic adhesiolysis and manipulation were performed, so the total number of the arthroscopic procedures ranged from 1 to 4. The ratio of the arthroscopic operation has been reported as 10.9%[22] and 15%.[21] In our study, except for 1 case who had 1 arthroscopic irrigation and debridement, 8 cases had the arthroscopic treatment more than 2 times. Assuming this is the feature of *M. massiliense* rather than the failure of the first arthroscopy, we suggest that the arthroscopic operation is more advantageous than the conventional open surgery. Further studies need to be done.

NTM adheres to the surface of the foreign body whose membrane is abundant with lipid.[28,29] The characteristic finding of the 9 cases in this study was the severe infection of the fat layer. Synovitis involving a thickened and hyperemic synovial membrane was evident in the joints of these patients. So, they were characterized as having severe fat tissue infection. As well as the severe infections of the fat tissue in the knee joint, they had abscess in the hypodermic fat layer around the area receiving some injections. The symptoms seemed to have persisted since the NTM could grow well and live long in the fat-enriched layer. In 6 cases, degenerative arthritis of K-L stage 4 was observed. Three of

the 6 cases needed to have an artificial joint replacement since their pain was not controlled by the medication.

No study has reported the prognosis after performing the artificial joint replacement for the patients infected with NTM including *M. massiliense*. Some studies have reported the result of the operation of the arthritis patients infected by TM. Kim reported that after treating 22 cases of the septic arthritis of the TM joints, the average time to perform the artificial joint replacement was 1 year, and in 3 cases (14%) recurrence occurred.[30] Su et al reported that after treating 16 cases of tuberculous arthritis, the average time to perform the artificial joint replacement was 2.1 years, with recurrence in 5 cases (31%).[31] However, Ozturkmen et al reported that in 12 cases of tuberculous arthritis no reinfection occurred after artificial joint replacement, with a good prognosis. The authors concluded that artificial joint replacement is not a taboo for tuberculous arthritis.[32] Therefore, whether to perform artificial joint replacement despite normal current blood test count or arthrocentesis test count, when to perform it, what kind of preventive antibiotics to select at the time of operation, and how much rate of reinfection to occur remains to be definitively clarified.

Twenty-seven patients were infected by irregular *M.* in 2012 after having an injection treatment in the primary care clinic in which a range of procedures and injection treatment had been performed. Among them, 9 patients were treated in our hospital.

Recently, the rate of occurrence of the side effects, such as the secondary infection around the injection area, has been increasing. This coincides with the increased use of injection treatment, including intrajoint injection, trigger point injection, prolotherapy, neuroplasty, nerve block, and intramuscular stimulation. According to Geirsson et al, 41.8% of the septic arthritis patients had disease onset after taking the injection treatment in the joint.[33] Therefore, precautions should be taken to prevent possible secondary infections. Disinfection around the injection area should be done aseptically, and the performer should wear sterile gloves. In addition, reuse of the syringe should not be allowed, and drugs like lidocaine or normal saline should not be reused. Every procedure should be performed by the practitioner.

The limit of this study is it is a retrospective study and difficult to generalize due to the small number of cases involved in the study. Nevertheless, considering the rarity of infection with irregular *M.*, and that, in particular, no study has been reported regarding the infection in the joint by *M. massiliense*, this study is significant in that it analyzed the clinical result of the combination therapy in which the antibiotic treatment and the arthroscopic operation were performed for the patients infected collectively with septic arthritis by *M. massiliense* in a single primary care clinic.

5. Conclusions

In this study, long-term antibiotic treatment was performed combined with the arthroscopic operation, accompanied by long term follow-up. NTM septic arthritis had a higher recurrence and a higher contracture incidence than septic arthritis caused by tuberculous mycobacteria or other bacteria. Treatment was possible with repeated arthroscopic debridement and intravenous antibiotics. This study is expected to help with the diagnosis and treatment of the possible occurrence of the joint infection by NTM.

Author contributions

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