

## CLINICAL ANALYSIS OF OSTEOARTICULAR NONTUBERCULOUS MYCOBACTERIAL INFECTION

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**Abstract** [Objective] The incidence rate of nontuberculous mycobacterial (NTM) infection has been increasing globally in recent years. However, reports of osteoarticular NTM infection are relatively rare. We report the characteristic clinical features of patients with osteoarticular NTM infection. [Patients and Methods] We examined 14 patients with osteoarticular NTM infection (mean age, 68 years) were treated in our hospital in the 20 years between 1995 and 2015. [Results] The rate of osteoarticular NTM infection in whole osteoarticular infection during the same period in our hospital was 2.7%. The NTM species isolated from the 14 patients included *Mycobacterium avium* (n=7), *M. intracellulare* (n=5), *M. fortuitum* (n=1), and *M. kansasii* (n=1). Twelve patients had spinal involvements, and their levels were categorized as thoracic (n=3), lumbar (n=4), thoracolumbar (n=1), and cervicothoracic (n=4), with an average number of affected vertebra of 4.4. Nine patients had pulmonary lesions, including fibrocavitary (n=5) and nodular/bronchiectatic types (n=4). Nine patients had lesions in sites other than the spinal and pulmonary regions, including the skin (n=6), rib (n=2), ilium (n=2), humerus (n=2), ulna (n=1), wrist (n=1), knee joint (n=1), femur (n=2), tibia (n=1), toe (n=1), and kidney (n=1). In the initial examination, 11 patients were misdiagnosed, which delayed the final diagnosis in 7 patients. Six patients received chemotherapy with rifampicin, ethambutol, and clarithromycin, and 8 patients received other macrolide-based therapy. Five patients underwent surgical treatments in former hospitals, and 8 patients underwent surgical treatments (including salvage surgeries) in our hospital. With regard to outcome, 9 patients achieved healing, 2 patients with relapse were healed after retreatment, 1 patient was undergoing treatment, 1 patient had interrupted treatment, and 1 patient died during the treatment period. [Discussion] Osteoarticular NTM infection presented widely spread lesions in the spine and other various locations, mostly developed as a part of disseminated infection. Most patients were aged or immunosuppressed, but some patients were healthy individuals with no relevant medical history. Thus, if a patient is diagnosed with disseminated NTM infection, examination for possible lesions in other sites, including the bone and joint, should be performed. Cutaneous lesions, including subcutaneous abscess, were also characteristic. It is worth mentioning that such lesions can develop even under chemotherapy. Given the increasing trend in the overall incidence of NTM infection, awareness that NTM is a causative organism of osteoarticular infection is important.

**Key words** : Nontuberculous mycobacterial infection, Osteomyelitis, Spondylitis, Arthritis, Disseminated infection

### Introduction

The incidence of nontuberculous mycobacterial (NTM) infection has been increasing globally, including Japan. Its prevalence in Japan is estimated to be 33–65 cases per 100,000 individuals, which is considered one of the highest in the world<sup>1)</sup>. The pathophysiological mechanism and treatment of NTM have not been clarified yet. Especially osteoarticular NTM infection, which is usually reported as a part of the pathology of disseminated NTM infection, is relatively rarely

reported in case series. We report the characteristic clinical features of 14 patients with osteoarticular NTM infection who were treated in our department.

### Patients and Methods

We examined 14 patients with osteoarticular NTM infection (age: range, 52–86 years; mean, 68 years) who were treated in our department within the 20 years between 1995 and 2015. Seven of the 14 patients were male. Diagnosis of osteoarticular NTM infection was made based on the detection of bacteria

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in the lesion specimens obtained during surgery or biopsy. However, in one case (case 12) with evident pulmonary NTM infection, the size and location of the lesions were not suitable for performing a biopsy. Hence, a diagnosis of osteoarticular NTM infection was made based on the clinical course and diagnostic imaging findings. We evaluated the clinical characteristics of osteoarticular lesions and their treatment outcomes in order to identify useful diagnostic and therapeutic features.

## Results

### (1) Patients characteristic (Table 1)

In our review of the database of osteoarticular infection treated in our department between 1995 and 2015, we identified 523 patients who had osteoarticular infection, including all of the pathogenic organisms (excluding postoperative infections). Therefore, the rate of osteoarticular NTM infection (n=14) was 2.7% (14/523 cases). The first seven cases occurred within the 15 years between 1995 and 2010, and the rate of the infection in this period was 2.0% (7/344 cases). While the remaining seven cases occurred within the 5 years between 2011 and 2015, the rate of the infection increased to 3.9% (7/179 cases), indicating an increasing trend in the recent years. NTM species isolated from the patients included *M. avium* (n=7), *M. intracellulare* (n=5), *M. fortuitum* (n=1), and *M. kansasii* (n=1). The spine was the most commonly affected region that was noted in the 12 patients. When assessed radiologically, the level of spinal involvement was categorized as thoracic (n=3), lumbar (n=4), thoracolumbar (n=1), and cervicothoracic (n=4), with an average number of affected vertebra of 4.4 (range, 2–14). Five patients had paravertebral gravitation abscesses. Eight patients presented with neurological involvement, including paralysis due to myelopathy (n=5) and radiculopathy (n=3). Nine patients

had pulmonary lesions (Table 2), including fibrocavitary (n=5) and nodular/bronchiectatic types (n=4). One patient (case 12) had a persistent smear-positive lesion. Nine patients had lesions located in sites other than the spinal and pulmonary region, including the skin (n=6), rib (n=2), ilium (n=2), humerus (n=2), ulna (n=1), wrist (n=1), knee joint (n=1), femur (n=2), tibia (n=1), toe (n=1), and kidney (n=1). The cutaneous lesion showed variations, including multiple subcutaneous abscess (cases 2, 7, and 9), eczema (cases 5 and 13), and large subcutaneous abscess (case 14). Three patients had comorbidities, including diabetes mellitus, liver cirrhosis, and polymyalgia rheumatica (PMR). None of the patients had human immunodeficiency virus (HIV) infection. Additionally, no patient was engaged in an occupation or in hobbies that may have resulted in exposure to the source of NTM infection. Laboratory data at the first examination showed that the mean C-reactive protein (CRP) level was  $4.1 \pm 4.0$  mg/dL, the mean white blood cell count was  $6488.6 \pm 4293.7/\mu\text{L}$ , and the mean lymphocyte count was  $1451.8 \pm 1096.2/\mu\text{L}$ . The expression level of serum IgA antibody to glycopeptidolipid core antigen specific for *Mycobacterium avium* complex (MAC)<sup>2)</sup> was measured by using Capilia® MAC Ab ELISA before the start of the treatment in 8 of the 12 patients, whose causative bacteria was MAC. Seven patients (87.5%) had positive results. The patient with a negative result did not have a pulmonary lesion. QuantiFERON® (QFT) was used in 9 patients for differential diagnosis of tuberculosis, of whom 4 showed positive control failure.

### (2) Diagnostic problems and treatments (Table 3)

In the initial examination, 11 patients were misdiagnosed with, for example, tuberculosis (n=3), osteoporotic fracture (n=2), metastatic tumor (n=1), osteoarthritis (n=1), subcutaneous abscess (n=1), rheumatoid arthritis (RA; n=1), PMR (n=1), and no lesion (overlooked lesion on radiography; n=

**Table 1** Clinical characteristics of the 14 patients with osteoarticular NTM lesions

| Case | Age (years)/sex | Year of diagnosis | Mycobacterium species    | Spinal lesion                 | Other NTM lesions                       | Comorbidity               |
|------|-----------------|-------------------|--------------------------|-------------------------------|---|---------------------------|
| 1    | 69M             | 1995              | <i>M. avium</i>          | T7–9                          | Fourth rib                              | —                         |
| 2    | 52F             | 1998              | <i>M. fortuitum</i>      | T8–12, L3                     | Kidney, subcutaneous                    | Diabetes mellitus         |
| 3    | 80M             | 2004              | <i>M. intracellulare</i> | L2–4                          | —                                       | —                         |
| 4    | 74M             | 2006              | <i>M. intracellulare</i> | C5/6, L5/S1                   | —                                       | Liver cirrhosis           |
| 5    | 55F             | 2006, Rec         | <i>M. avium</i>          | C1/2, T1, 6, 11, 12, L2–4     | Sacro-iliac joint, ninth rib, cutaneous | —                         |
| 6    | 83F             | 2009              | <i>M. intracellulare</i> | T10–12                        | —                                       | —                         |
| 7    | 69M             | 2010              | <i>M. avium</i>          | C6, T2, 3, 9, 10–12, L1–5, S1 | Subcutaneous                            | —                         |
| 8    | 86F             | 2011              | <i>M. avium</i>          | L2–4                          | —                                       | —                         |
| 9    | 83F             | 2011              | <i>M. avium</i>          | C6–T1                         | Humerus, femur, subcutaneous            | —                         |
| 10   | 52M             | 2013, Rec         | <i>M. kansasii</i>       | T10/11                        | —                                       | —                         |
| 11   | 54F             | 2012              | <i>M. intracellulare</i> | —                             | Knee joint                              | —                         |
| 12   | 71M             | 2013, Rec         | <i>M. avium</i>          | L4, S2                        | Femur, ilium                            | After lung cancer surgery |
| 13   | 65M             | 2013, Rec         | <i>M. intracellulare</i> | —                             | Tibia, ulna, cutaneous                  | —                         |
| 14   | 64F             | 2015              | <i>M. avium</i>          | L1, 3                         | Shoulder, wrist, toe, subcutaneous      | PMR, IP                   |

Rec: recurrence, PMR: polymyalgia rheumatica, IP: interstitial pneumonia

1). These misdiagnoses delayed the final diagnosis in 7 patients. Although 4 patients underwent retreatment of NTM infection, none of them had a relapse of osteoarticular NTM lesions. Six patients received chemotherapy with rifampicin (RFP), ethambutol (EB), and clarithromycin (CAM), and 8 patients received other macrolide-based therapies. Five patients underwent surgical treatments in former hospitals, including laminectomy (n=1), anterior spinal fusion (n=2), curettage (n=1), and posterior fixation (n=1). Eight patients underwent surgical treatments (including salvage surgeries) in our hospital, including anterior spinal fusion (n=5), curettage (n=2), and drainage (n=1). Three patients were treated conservatively. The duration of chemotherapy ranged from 12 to 24 months (mean, 17.7 months), except in one patient who was undergoing current treatment. Healing of the osteoarticular lesion was judged by integrating findings such as bone formation surrounding osseous lesions on radiography, normalization of the intensity change in magnetic resonance imaging (MRI), closure of fistula in cutaneous lesions, and reduction of the inflammatory response. With regard to outcome, 9 patients achieved healing, 2 patients with a relapse were healed after retreatment, 1 patient was undergoing treatment, 1 patient had interrupted treatment (persistent smear-positive results), and 1 patient died during treatment.

### Case presentation

#### (1) Case 13

A 65-year-old man developed right pretibial pain of unknown origin and visited a local clinic, lower leg radiography revealed no abnormal findings. Fourteen months previously, he developed NTM (*M. intracellulare*) infection of the right ulnar olecranon and scalp, and completed 6 months of treatment with RFP, EB, and CAM in a local hospital. He had been observed for 2 months for the right pretibial pain. Then, he visited a local hospital because of persistent pain. On MRI,

an abnormal intensity area in the diaphysis of the right tibia was detected (Fig. 1a). The lesion was suspected as NTM infection because of his medical history. He was then referred to our department. On physical examination, he had no fever and swelling or tenderness in his right pretibial area, but had reddish hives scattered over both his lower legs. Two large patches of eczema were on his scalp (Fig. 1b), which were relapsed lesions of the previous treatment. The right ulnar lesion did not relapse. Laboratory data showed a CRP level of 0.67 mg/dL, a sedimentation rate of 66 mm/h, a white blood cell count of 4900/ $\mu$ L, a lymphocyte count of 1000/ $\mu$ L, and a serum MAC antibody of 2.75 U/mL. Diagnostic imaging revealed no apparent pulmonary lesion, and a sputum test result was smear-negative for NTM. Three months after the onset of pain, curettage was performed by fenestration of the anterior tibial cortex. The lesion was completely confined to the bone marrow cavity, showing yellowish-translucent pus and sequestra (Fig. 1c). After sufficient surgical excision of the diseased tissue and saline irrigation, a defect in the bone marrow was filled with hydroxyapatite paste, and then the

**Table 2** Statuses of the 9 patients with pulmonary NTM lesions

| Case | Classification | Laterality | Disease extent |
|------|----------------|------------|----------------|
| 1    | NB             | Uni        | 1              |
| 3    | FC             | Uni        | 2              |
| 4    | NB             | Bil        | 2              |
| 5    | NB             | Uni        | 1              |
| 7    | FC             | Uni        | 2              |
| 8    | FC             | Uni        | 2              |
| 9    | NB             | Uni        | 1              |
| 10   | FC             | Bil        | 2              |
| 12   | FC             | Uni        | 2              |

FC: fibrocavitary, NB: nodular/bronchiectatic

Bil: Bilateral, Uni: Unilateral

Disease extent is classified according to the Japanese Tuberculosis Association classification system.

**Table 3** Diagnostic problem and treatment in the 14 patients with osteoarticular NTM lesions

| Case | Misdiagnosis              | Anti-NTM drug      | Surgery       | Treatment duration (months) | Outcome                   |
|------|---------------------------|--------------------|---------------|-----------------------------|---------------------------|
| 1    | Metastatic tumor          | H, E, CAM, SPFX    | Spinal fusion | 12                          | Healed                    |
| 2    | —                         | E, X               | Spinal fusion | 24                          | Healed                    |
| 3    | Tuberculosis              | R, E, CAM          | Spinal fusion | 12                          | Healed                    |
| 4    | Tuberculosis              | R, E, CAM          | Spinal fusion | 12                          | Healed                    |
| 5    | Tuberculosis              | R, CAM, AMK, MFLX  | Spinal fusion | 19                          | Healed                    |
| 6    | —                         | R, E, CAM          | Spinal fusion | 24                          | Healed                    |
| 7    | Osteoporotic fracture     | R, CAM, X          | Spinal fusion | 12                          | Healed                    |
| 8    | Osteoporotic fracture     | R, E, CAM          | —             | 13                          | Died                      |
| 9    | Subcutaneous abscess      | R, E, CAM          | Curettage     | 24                          | Healed                    |
| 10   | —                         | CAM, MFLX          | —             | 12                          | Healed                    |
| 11   | Osteoarthritis            | R, E, CAM          | Curettage     | 18                          | Healed                    |
| 12   | Polymyalgia rheumatica    | RBT, CAM, X        | —             | 24                          | Persistent smear-positive |
| 13   | Overlooked on radiography | R, E, CAM, AMK, KM | Curettage     | 24                          | Healed                    |
| 14   | Rheumatoid arthritis      | E, CAM, AMK, SM    | Drainage      | 4                           | Under treatment           |

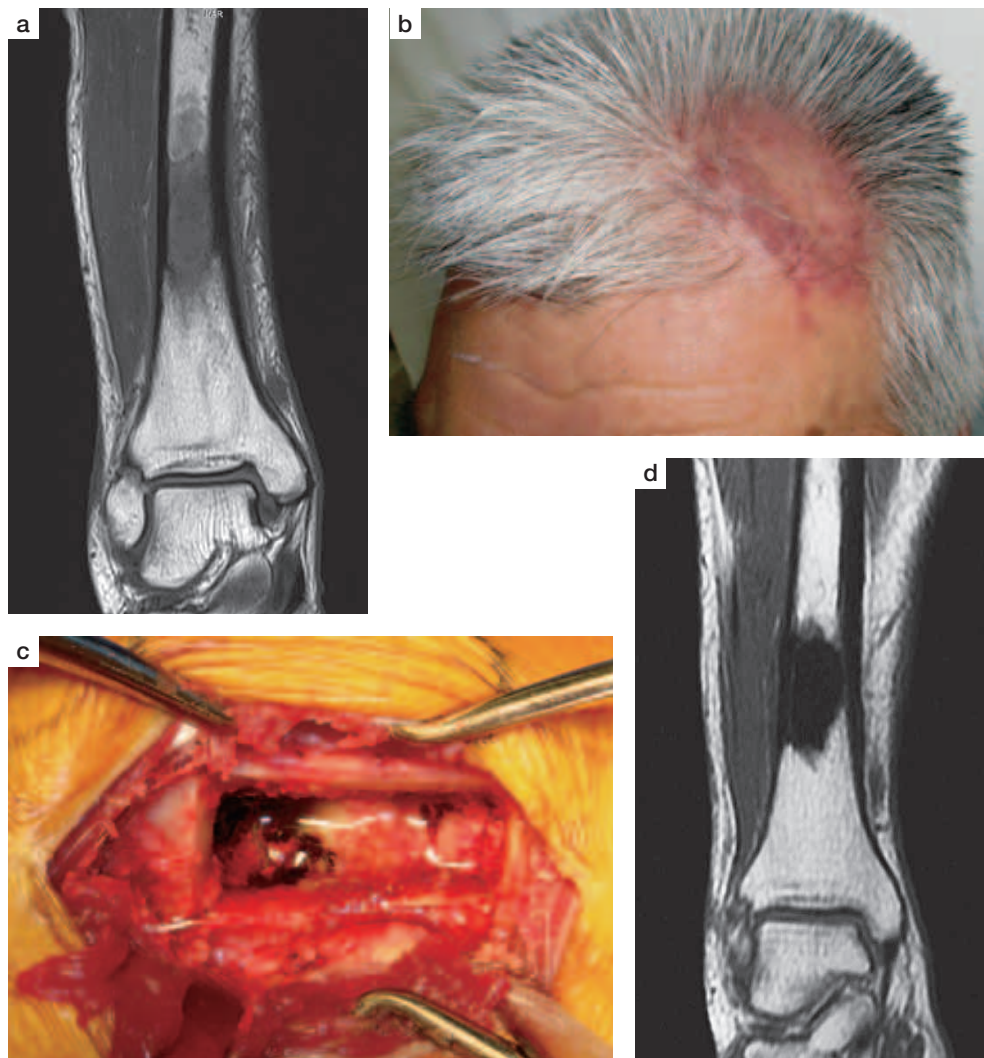
H: isoniazid, E: ethambutol, CAM: clarithromycin, SPFX: sparfloxacin X: levofloxacin, R: rifampicin, AMK: amikacin, MFLX: moxifloxacin, RBT: rifabutin, KM: kanamycin, SM: streptomycin

bone cortex that was excised at first was inlaid in the same location. As *M. intracellulare* was detected in the intraoperative specimen, treatment with RFP, EB, and CAM was restarted in combination with amikacin (AMK) because of the recurrence. AMK was continued for 2 months after the surgery until switching to kanamycin because of the increasing creatinine level. The cutaneous lesions in the scalp and legs were gradually improved after the restart of chemotherapy, the CRP level decreased and turned negative 3 months after the surgery, bone union of the surgical site was achieved 6 months after the surgery, and MRI revealed normalization of the bone marrow intensity 1 year after the surgery (Fig. 1d). Chemotherapy was completed 24 months after the surgery, and so far, no relapse of the NTM infection has been detected.

(2) Case 14

A 64-year-old woman developed swelling of her right wrist,

right great toe metatarsophalangeal (MTP) joint, left second toe MTP joint, right ankle joint, and left scapular region 5 years prior. She had histories of interstitial pneumonia (IP) and PMR since she was 40 years old, which were treated continuously with prednisolone. Eight years previously, she was diagnosed with seronegative RA, which caused the right wrist pain and swelling. In order to treat the multiple joint swelling that had developed 5 years previously, which was considered as an exacerbation of the RA, methotrexate, infliximab, tocilizumab, and other antirheumatic drugs were used, but no improvement was observed. The swollen left second toe MTP joint and left scapular region were punctured several times for detection of bacteria, all of which turned out negative results. However, culture for *Mycobacterium* was not ordered at all. Consequently, the left second toe MTP joint formed a fistula with continuous serous discharge. The



**Fig. 1** Case 13

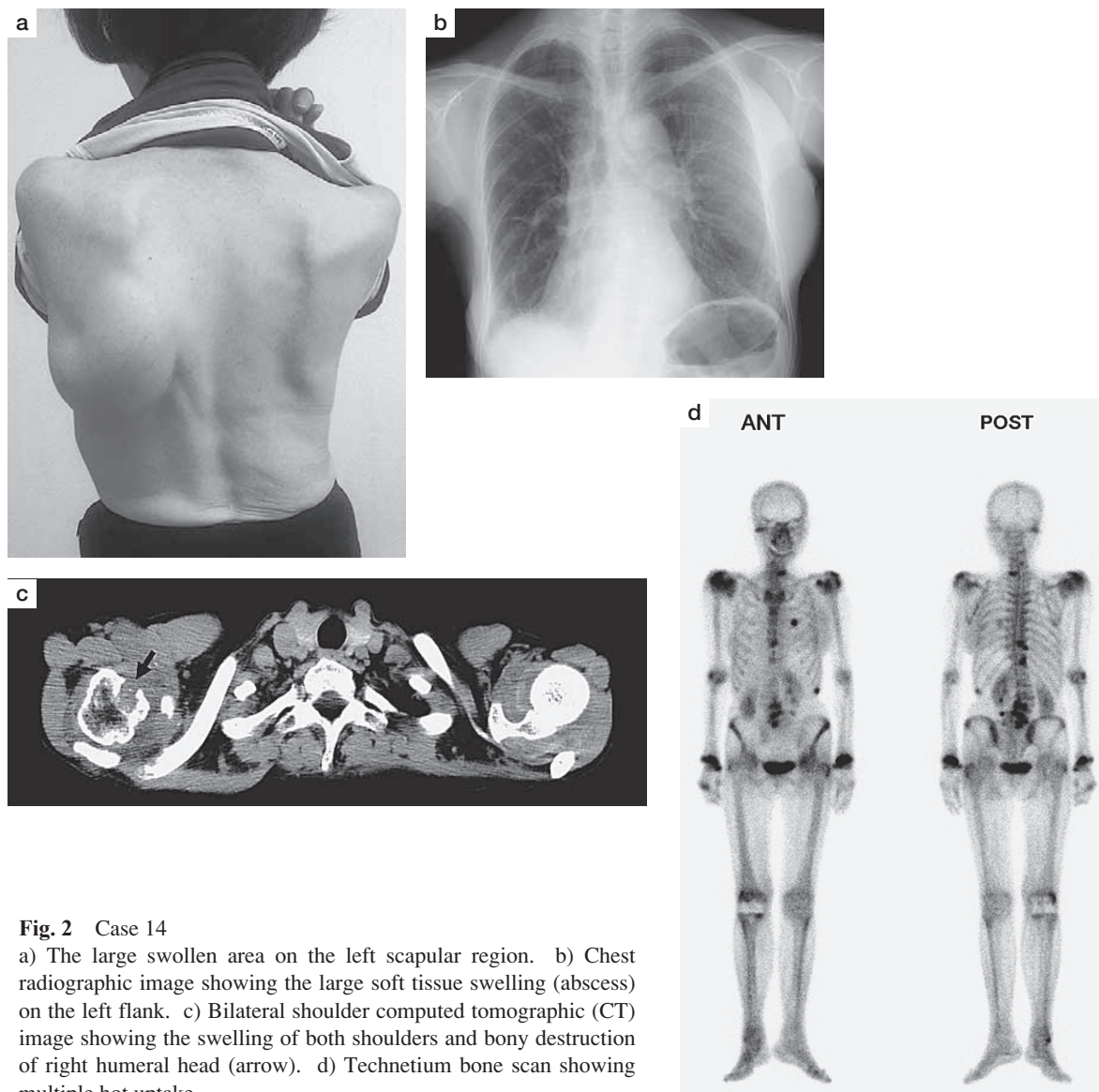
a) Preoperative magnetic resonance image (MRI) showing the intramedullary lesion of the tibia. b) The scalp lesion at initial examination. c) Intraoperative photograph of the intramedullary lesion of the tibia. d) Postoperative MRI of the tibia showing disappearance of the inflammatory change (a low intensity area indicates the hydroxyapatite paste used to fill in the curetted area).

swelling in the left scapular region gradually increased and became a fist-size mass (Fig. 2a). The swollen joint was punctured because of tense feeling increased. Finally, mycobacterial examination of the aspirated fluid was performed, and the results obtained were positive for *M. avium*. Thereafter, she was referred to our department. On physical examination, she had no fever, laboratory data showed a CRP level of 1.92 mg/dL, a sedimentation rate of 28 mm/h, a white blood cell count of 8080/ $\mu$ L, a lymphocyte count of 300/ $\mu$ L, and a serum MAC antibody of 0.74 U/mL. Diagnostic imaging revealed no apparent pulmonary NTM lesion, but findings showed stable IP (Fig. 2b) and the result of the sputum test was smear-negative for NTM. Computed tomography (CT) revealed obvious bone destruction in the right humeral head (Fig. 2c). Technetium bone scintigraphy revealed many hot uptakes in various locations, including visibly swollen joints (Fig. 2d). *M. avium* was detected with aspirated fluid from the right wrist, right great toe MTP joint, right ankle joint,

and both shoulder joints. Therefore, she was diagnosed with disseminated MAC infection. Treatment with EB, CAM, and AMK was started. One month after the start of the chemotherapy, drainage of the left scapular region subcutaneous abscess was performed, thereby 400 mL of yellowish pus with a lot of debris was drained. The abscess was a pure subcutaneous abscess rather than a gravitation abscess from the osteoarticular lesion. AMK was discontinued after 4 weeks of administration and switched to streptomycin. The patient's current treatment is ongoing.

### Discussion

Osteoarticular NTM infection mostly develops as a part of disseminated infection and has been known more than a century ago. *M. avium*, as is clear from its nomenclature, was studied initially as a pathogen in birds. Koch reported on NTM infection evaluated from autopsy samples from a vast number and types of birds in 1907<sup>3)</sup>. The lesions in most of



**Fig. 2** Case 14

a) The large swollen area on the left scapular region. b) Chest radiographic image showing the large soft tissue swelling (abscess) on the left flank. c) Bilateral shoulder computed tomographic (CT) image showing the swelling of both shoulders and bony destruction of right humeral head (arrow). d) Technetium bone scan showing multiple hot uptake.

the autopsy cases spread over multiple organs (i.e., disseminated infection). As bones and joints were cited as locations of infection, Koch's report is probably the first report of osteoarthritis caused by NTM. However, NTM as a human pathogen has been described more recently. In 1943, human pulmonary NTM infection was reported in detail for the first time by Feldman<sup>4)</sup>. Human disseminated NTM osteomyelitis has been reported since the 1950s<sup>5)6)</sup>. It used to commonly develop in patients with immunodeficiency condition<sup>7)8)</sup>, but an increasing number of patients showed no such background<sup>9)–11)</sup>. In this study, most of the patients were aged or immunosuppressed but not severely immunocompromised, whereas some of the patients were healthy individuals with no relevant medical history.

In this manner, cases of NTM infection have been emerging gradually in recent years, although its cause is not well understood. In association with its increase, the incidence of osteoarticular NTM infection is also considered to be increasing, but its prevalence remains unclear. McHenry reported a long-term outcome in patients with vertebral osteomyelitis who attended 7 facilities of the region from 1950 to 1994, wherein NTM was detected as a causative organism in 1 (0.4%) of 253 patients<sup>12)</sup>. Given that the data are limited up to 1994 and the incidence of NTM infection in the United States shows an increasing trend<sup>13)</sup>, the incidence of osteoarticular lesions should have increased in recent years. Considering that the estimated incidence of NTM infection in New York during the period 2000–2003 was 2.7 cases per 100,000 individuals<sup>14)</sup> and that in Japan in 2001 was 5.9 cases per 100,000 individuals<sup>1)</sup>, the incidence rate of NTM infection in our department during the last 5 years (3.9%) is somewhat high. This is probably because our hospital has specialized in mycobacterial infection for years. Furthermore, our region is ranked as having the highest incidence of tuberculosis in Japan for many years.

Most patients in this case series presented disseminated infection. Two patients developed 1 lesion, 3 patients developed 2 lesions, and the remaining 9 patients developed three or more lesions. This is clearly a high incidence rate of disseminated lesions compared with osteoarticular infection with *Mycobacterium tuberculosis*. Spinal lesions were characteristically extensive with 4.4 vertebrae affected on average. In addition, a high rate of cervical involvement was also a notable feature (4 [33%] of the 12 patients). The onsets were insidious, and the initial symptoms were relatively mild considering the extent of the lesions, which consequently lead to diagnostic delays. Thus, a patient with disseminated NTM infection should undergo whole-body examination for possible lesions in other sites, including the spine or other osteoarticular regions. In particular, osteoarticular NTM infection in a patient with a collagen disease, such as case 14, is difficult to diagnose, unless bacterial examination by joint puncture is performed. Kanik reported a patient with NTM arthritis who had been treated for seronegative RA for 2.5

years until final diagnosis based on synovial fluid culture findings<sup>15)</sup>. Recently, use of immunosuppressive agents such as biologics to treat such patients has increased. Care should be taken for detecting NTM infection in such patients, as routine screening for tuberculosis is not useful for such cases.

Cutaneous lesion was also a distinctive feature (6 [42.9%] of 14 patients). Although NTM species such as *M. fortuitum* or *M. abscessus* are commonly detected in the cutaneous lesion, most NTM species can be causative organisms<sup>16)17)</sup>. In spite of the rarity of cutaneous tuberculosis, bone and skin development in disseminated NTM infection is one of the common features<sup>7)18)–20)</sup>. Horsburgh reported 17 patients (46%) with cutaneous lesions and 5 patients (14%) with osseous lesions in their study of 37 patients with disseminated NTM infection<sup>21)</sup>. Ingram reported 9 patients (17%) with cutaneous lesions and 40 patients (74%) with osseous lesions in their study of 54 patients with disseminated NTM infection<sup>22)</sup>. The etiology of localization to the skin and bone in disseminated NTM infection is still unclear. However, Arend speculated that the relative scarcity of macrophages in normal skin and bone tissue could be an underlying part of the tissue-specific susceptibility<sup>23)</sup>.

Recently, interferon (IFN)- $\gamma$  productivity or autoantibody against IFN- $\gamma$  has been suspected as a cause of the development of disseminated NTM infection<sup>23)–25)</sup>. Meanwhile, gene mutations as the cause of IFN- $\gamma$  deficiency have also been reported<sup>23)26)</sup>. In this study, 4 (44.4%) of 9 patients who had undergone a QFT test showed positive control failure, suggesting the presence of immunoresponse deficiency. Okimoto studied the positive response rate to QFT in patients with MAC infection, and 4.2% of the patients showed positive control failure<sup>27)</sup>, which is a much lower rate than the one in our study. However, the number of patients in this study was too small, and normal responses to positive control were obtained in the remaining 5 patients. Thus, reexamination of this issue with more subjects in the future is necessary.

In our literature search, we found no well-documented case series that describes about treatment of osteoarticular NTM infection in recent years. Aberg reported 48 HIV patients with disseminated MAC infection who were treated with 1 year of chemotherapy (including 2 patients with spinal lesion), of whom only 1 patient developed localized osteomyelitis after withdrawal of the therapy<sup>28)</sup>. Marchevsky reported 8 patients with NTM osteomyelitis, of whom 6 responded well to surgical excision alone without recurrence and 2 developed MAC infection and were treated with a combination of surgery and chemotherapy<sup>29)</sup>. However, none of the patients had disseminated NTM infection. In general, surgical outcome of osteoarticular NTM infection has been reported to be favorable<sup>17)30)</sup>, as is shown in this study. Surgery should be performed as long as the general condition of the patient permits. Chemotherapy with adequate drug combination and enough duration was considered mandatory for the treatment of osteoarticular NTM infection in its disseminated form. For

example, case 13 had a relapse after the 6-month treatment, and case 9 developed subcutaneous abscesses repeatedly even at 1 year after the start of the chemotherapy, showing a discrepancy with well healed spinal lesions. In addition, if we exclude the 5 patients who received retreatments (cases 5 and 13), the patient whose treatment was interrupted (case 12), the patient who is receiving treatment (case 14), and the patient whose lesions healed recently (case 9), the lesions healed because of the initial treatment in only four out of 9 patients with disseminated NTM infection (case 1, 2, 4, and 7). Furthermore, considering that disseminated NTM infection is generally refractory, the clinical outcomes noted in this study should be carefully interpreted because recurrence may occur subsequently in these four patients. Therefore, the duration of chemotherapy for osteoarticular NTM infection should be carefully determined by considering if all lesions in the body have been healed. In addition, we should always consider the possibility of a relapse even for cases of successful treatment.

### Conclusion

The incidence of osteoarticular NTM infection has shown an increasing trend. Thus, it is necessary to keep in mind that it could be complicated with pulmonary NTM infection, as a part of the disseminated infection. The spine was the most common and extensively involved site. Cutaneous lesions, including subcutaneous abscess, were also characteristic features. Considering the difficulties in diagnosis and treatment, as well as the increasing trend of the overall incidence of NTM infection, awareness of NTM as a causative organism of osteoarticular infection is important.

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### Conflict of interest

The authors declare that there is no conflict of interest related to this article.

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