Clinical and laboratory observations

Title; Septic arthritis caused by *Mycobacterium kansasii* in a bone marrow transplant recipient

Minako Sugiyama[1], Yukayo Terashita[1], Kazuya Hara[1], Yuko Cho[1], Tsuyoshi Asano[2], Akihiro Iguchi[1]

[1] Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan

[2] Department of Orthopaedic Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence: Minako Sugiyama, Department of Pediatrics, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo 060-8638, Japan.

E-mail: s-minako@huhp.hokudai.ac.jp

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Key words: nontuberculous mycobacterial arthritis; *Mycobacterium kansasii*; hematopoietic stem cell transplantation (HSCT); graft-versus-host disease (GVHD); acute lymphoblastic leukemia (ALL)

ABSTRACT

We report an 18-year-old female with septic arthritis due to *Mycobacterium kansasii*. Three years and 6 months before the arthritis, the patient underwent bone marrow transplantation and developed severe chronic graft-versus-host disease. The arthritis was refractory to medication, and she underwent joint lavage of the right foot, hip joint, and elbow joint. After surgery, her joint symptoms were relieved, and chronic graft-versus-host disease remitted more easily. It is important that we maintain a high index of suspicion for mycobacterial arthritis and diagnose it early when immunosuppressed patients experience chronic pain and joint swelling.

Abbreviations

nontuberculous mycobacterium, NTM; HSCT, hematopoietic stem cell transplantation; BMT, bone marrow transplantation; T- ALL, T-cell acute lymphoid leukemia; MTX, methotrexate; GVHD, graft-versus-host disease; cGVHD, chronic graft-versus-host disease; TMA, thrombotic microangiopathy; MMF, mycophenolate mofetil; PSL, prednisolone; MRI, magnetic resonance imaging; T2w-STIR, T2-weighted short-tau inversion recovery; IFN-γ, interferon gamma; MIC, minimum inhibitory concentration; CAM, clarithromycin; RFP, rifampicin; EB, ethambutol; INH, isoniazid; AIDS,

19 acquired immunodeficiency syndrome; TNF, tumor necrosis factor

20

21 **INTRODUCTION**

22 *Mycobacterium kansasii* is a nontuberculous mycobacterium (NTM). Although
23 nontuberculous mycobacterial infections are typically pulmonary infections, various
24 organs, including the skin, brain, liver, and bone marrow, can be affected [1]. In Japan,
25 the incidence of pulmonary nontuberculous mycobacterial disease was estimated to be
26 14.7 cases per 100,000 person-years in 2015 [2].

27 Immunosuppressed patients, including hematopoietic stem cell transplantation
28 (HSCT) recipients, especially allogeneic HSCT recipients, are at increased risk of
29 nontuberculous mycobacterial infection [1,3,4]. Unal, et al. reported that the incidence
30 of NTM infection in pediatric patients who received allogeneic HSCT was 6.4% [3].
31 We report a case of disseminated NTM infection. Although there is few report about
32 arthritis caused by *M. kansasii* in HSCT recipients, appropriate approach for arthritis in
33 HSCT recipients may not be performed. The infection could exacerbate the patient's
34 cGVHD (chronic graft-versus-host disease), and it cause increasing requisite amounts of
35 immunosuppressive agents. We must diagnose this infection to prevent the negative
36 spiral early.

CASE REPORT

The patient was an 18-year-old Japanese female. At 12 years of age, she presented to our department with significant hepatomegaly and splenomegaly. Her laboratory test findings were as follows: white blood cell count, 924.0 × 10^9/L; red blood cell count, 1.47 × 10^9/L; hematocrit, 16.1%; hemoglobin, 5.1 g/dL; and platelet count, 5.6×10^9/L. Bone marrow aspiration showed hypercellularity with 94% peroxidase-negative blasts. Immunophenotyping revealed a variety of T-cell-specific antigens, since cells were positive for CD2, CD3, cyCD3, CD5, CD7, cy-TdT. These findings were consistent with a diagnosis of T-cell acute lymphoblastic leukemia (T-ALL). Central nervous system involvement was ruled out by first lumbar puncture. She was treated according to the high-risk arm of the Japan Association of Childhood Leukemia Study ALL-02. Although the initial response of her leukemia to prednisolone was not good, remission was achieved after initial induction therapy. We confirmed complete response by microscopic examination and flow cytometry. We could not perform minimal residual disease test. HSCT was planned for the patient at 13 years of age, 11 months after the diagnosis of T-ALL. Since there were no human leukocyte antigen-matched related donors, the patient received bone marrow from an unrelated

female donor. The patient and donor were shown to be one-locus (DR-locus) mismatched at A, B, C and DRB1 loci by sequencing-based DNA typing. Myeloablative conditioning consisted of etoposide (30 mg/kg) on day −7, 4-Gy total body irradiation on days −6 to −4 (total dose, 12-Gy), and cyclophosphamide (60 mg/kg) on days −3 and −2 (total dose, 120 mg/kg). The patient received intravenous infusion of bone marrow cells (total of 2.9×10^8/kg, 2.1×10^6/kg as CD34+ cells) after the conditioning. Tacrolimus (0.02 mg/kg) daily from day −1 and short-term methotrexate (MTX) (15 mg on day +1 and 10 mg on days +3, +6, and +11) were used for GVHD prophylaxis. The patient achieved engraftment (neutrophil count, $> 0.5 \times 10^9$/L) on day +20, and full-donor chimerism was detected using short tandem repeat analysis on day +36 after BMT. Although pre-engraftment syndrome and stage 2 acute cutaneous GVHD developed on day +10, the symptoms disappeared after administration of immunosuppressive agents including methylprednisolone and additional MTX. However, cGVHD of the skin, oral mucosa and lungs was observed. In addition, glucose intolerance, renal dysfunction, and thrombotic microangiopathy (TMA) progressively developed during a period of 2 years after bone marrow transplantation (BMT). Although we changed tacrolimus to mycophenolate mofetil (MMF) during this period, we had to stop MMF treatment due to progressed renal dysfunction and

hematopoietic disorder, mainly thrombocytopenia with bleeding symptoms. Therefore, the patient required prednisolone (PSL) (from 0.25 to 0.5 mg/kg) after BMT. In addition, she received immunoglobulin replacement due to delayed immune reconstitution. Although she sometimes complained morning stiffness of joints, joint swelling was not revealed. The stiffness of joints was diagnosed as caused by cGVHD. There was no chance which she was received joint puncture and suspected of bacteremia.

The patient complained of right foot pain beginning 3 months after BMT. T1 and T2-weighted magnetic resonance imaging (MRI) revealed low intensity on the navicular articular surface of the talus, and T2-weighted short-tau inversion recovery (T2w-STIR) imaging revealed high intensity in the region. We suspected osteonecrosis or arthritis caused by cGVHD and prolonged PSL administration rather than some type of infection. In addition, one year and 6 months after BMT, T2w-STIR imaging revealed high intensity on the right second and third metatarsal bones (Fig. 1a)

She had severe renal dysfunction and vesical bleeding due to thrombocytopenia at that time. Therefore, we did not attempt to obtain a biopsy specimen for culture and histopathological examination for fear of bleeding, infections, and side effects of general anesthesia. Three years after BMT, she experienced septic arthritis of the right

hip joint due to *Listeria monocytogenes*. She underwent arthroscopic lavage and treatment with tazobactam/piperacillin hydrate and meropenem serially for one month. Then, an enzyme immunoassay showed that serum interferon gamma (IFN-γ) level was not elevated, < 0.1 IU/mL. The destruction of her right caput femoris advanced, preventing her from standing.

Five months after bacterial arthritis had developed, and 3 years and 6 months after BMT, the patient experienced slight pain in the right hip joint again and developed fever consecutively. Her right hip and right elbow joints had become swollen. An MRI examination revealed a multiloculated cyst-like structure around the joints. A T1-weighted image showed low intensity, whereas T2-weighted MRI and T2w-STIR showed unequal high intensity (Fig. 1b, c). In addition, osteonecrosis of the right femoral head and transformation of the distal end of the humerus were noted. Synovial fluid obtained by arthrocentesis was cultured for mycobacteria and *M. kansasii* was identified. The bacterium was detected in both synovial fluid and blood culture. Then, the patient's chest computed tomography was normal. Although her skin was rough due to cGVHD, there is no lesion suspected of NTM infection. The minimum inhibitory concentration (MIC) of clarithromycin (CAM) was 0.25 μl/ml, and those of rifampicin (RFP) and ethambutol (EB) were 0.125 and 4 μl/ml, respectively. The MIC of isoniazid

(INH) was not determined. Results of chest computed tomography were normal, and serum IFN-γ level was slightly elevated at 0.2 IU/mL (normal, < 0.1 IU/mL). Conversely, decreases in CD4+ (209/μL) and CD8+ T cell counts (72.3/μL) were observed. We immediately started to administer CAM, RFP, and EB adapted to her renal function. We started also INH ten days after the initiation of CAM, RFP and EB. Then, because she revealed chronic renal dysfunction (creatinine clearance; 20.0ml/min/1.73m^2), she was administered CAM (400mg, 11mg/kg), RFP (450mg, 12.5mg/kg) daily, EB (500mg, 14mg/kg) once every 36 hours, INH (200mg, 5.5mg/kg) once every 48 hours orally. The interval of fever and joint swelling became progressively shorter despite frequent joint punctures. The distal interphalangeal joint of her right second finger and the dorsum of her right foot were also swollen (Fig. 1d). The site of right foot swelling was coincident with the painful region for 3 years. Two more weeks after, *M. kansasii* was not identified in blood culture, but synovial fluid obtained by arthrocentesis of right hip joint and the dorsum of right foot revealed *M. kansassii.* We determined that the mycobacterial arthritis was refractory to medical therapy, and she underwent joint lavage, debridement and sequestrectomy of the right foot, hip joint, and elbow joint 1 month after the beginning of medication. *M. kansasii* was detected in cultures from all surgical sites. After surgery, she had no fever, and *M. kansasii* was not

detected in synovial fluid obtained by arthrocentesis even though her right hip joint was slightly swollen. One year after the arthritis, her cGVHD, including symptoms such as renal dysfunction and stomatitis, remitted more easily, and her platelet count increased gradually. The dose of PSL was gradually decreased once. Serum IFN-γ level was not elevated, and low CD4+ (143/μL) and CD8+ T cell counts (100/μL) were still observed. Three years after the septic arthritis by *Mycobacterium kansasii*, the patient had died of lung cGVHD.

DISCUSSION

There have been only a few reports of septic arthritis due to *M. kansasii* even in immunosuppressed patients. Although our patient had slight pain in her right foot for about 3 years after BMT, it was difficult for us to reach a diagnosis of mycobacterial arthritis. Considering the clinical course over the period of 3 years, chronic inflammation caused by *M. kansasii* might have led to the exacerbation of her TMA and cGVHD. Her general status improved once after surgery though we could not prevent the progression of lung cGVHD. Together, the patient might suffer from NTM infection from 3 months after BMT, when she complained of right foot pain.

Immunosuppressed patients, such as HSCT recipients and patients with

145 autoimmune disorders or acquired immunodeficiency syndrome (AIDS), have an
146 increased risk of nontuberculous mycobacterial infection [1,3,4]. The incidence of
147 mycobacterial infections, including mycobacterium tuberculosis, has been reported to
148 be less than 5% in HSCT recipients [1,3]. Cordonnier et al. reported that eight patients
149 developed microbiologically proven NTM infection and that two of them died. One of
150 them died due to septic shock caused by *Mycobacterium avium* on day +122 after
151 transplantation, and the other patient who had severe cGVHD died 13 months after
152 transplantation due to septic shock caused by *Mycobacterium chelonae*. Unal et al.
153 identified nontuberculous mycobacterial infections in 5 (3.8%) of 132 pediatric
154 recipients. One of the five patients, a 2-year-old boy, was diagnosed with probable skin
155 and soft tissue infection by *M. kansasii*. In addition, two of the five patients had active
156 GVHD at the time nontuberculous mycobacterial infection was diagnosed [3]. As with
157 our patient, recipients who are administered prednisone due to cGVHD may be
158 predisposed to severe nontuberculous mycobacterial infections. The previous study
159 showed that patients who had died from mycobacterial infections had a more acute
160 clinical course than did patients who survived [1].

161 In another study, 37 cases of tuberculosis and 211 cases of nontuberculous
162 mycobacterial infection were found among 56,269 elderly patients with rheumatoid

arthritis. It was shown in that study the current anti-tumor necrosis factor (TNF) users had a significantly higher risk of nontuberculous mycobacterial infection than did non-users (odds ratio [OR] = 2.42) and that high-dose corticosteroid use also increased the risk of NTM infection (OR = 1.60) [4]. The production of IFN-γ was reported to be downregulated by infliximab in patients with active steroid-dependent or fistulizing Crohn's disease [5]. Although IFN-γ and TNF-α levels were reported to be elevated in recipients with chronic GVHD compared with those in patients without GVHD [6], it was shown that corticosteroid treatment caused a significant dose-related decrease in IFN-γ production [7]. Since anti- IFN-γ autoantibody is also strongly associated with NTM infections [8], the serum level of IFN-γ in patients with NTM infection needs to be determined. Although the IFN-γ level in our patient was slightly elevated after *M. kansasii* infection had been identified, 5 months before and 1 year after the arthritis, it was not elevated despite chronic inflammation due to GVHD. Prolonged administration of prednisolone might decrease its levels as well as decreasing CD4+ and CD8+ T cell counts. If the serum level of IFN-γ in a patient with NTM infection is low, and IFN-γ autoantibody is high, the patient will need more immunosuppressive agents. Recently, a few interleukins, including IL-2, IL-9, IL-13, and IL-17 have been indicated to diagnosis NTM infections, and to follow the therapeutic effect [9].

A few cases of arthritis due to *M. kansasii* have been reported, mainly elderly people or patients with systemic lupus erythematosus, rheumatoid arthritis, or AIDS [8, 10, 11], and the target joints were different. The clinical features were chronic pain and joint swelling, and most of the patients had no fever. The MRI findings were non-specific, suggesting synovitis and osteonecrosis. Only culture of synovial fluid obtained via arthrocentesis or blood may lead to a diagnosis. In our case, it was difficult to diagnose septic arthritis due to *M. kansasii* until multiple joints had become affected.

For patients with *M. kansasii* lung disease, daily treatment with 10 mg/kg/day RFP (maximum, 600 mg), 15 mg/kg/day EB, 5 mg/kg/day INH (maximum, 300 mg), and 50 mg/day pyridoxine is recommended [12]. The treatment duration should include 12 months of negative sputum cultures. The treatment regimen for disseminated infection should be the same as that for pulmonary disease. The duration should match that in patients infected with *Mycobacterium avium* complex, who are treated for at least 6-12 months after immune restoration. In our patient, there was no likelihood of discontinuing the antimycobacterial drugs because we could not decrease the dose of PSL due to severe cGVHD.

CONCLUSION

Although septic arthritis caused by *M. kansasii* is extremely rare, it is important that we maintain a high index of suspicion for mycobacterial arthritis and diagnose it early when patients have chronic pain and joint swelling.

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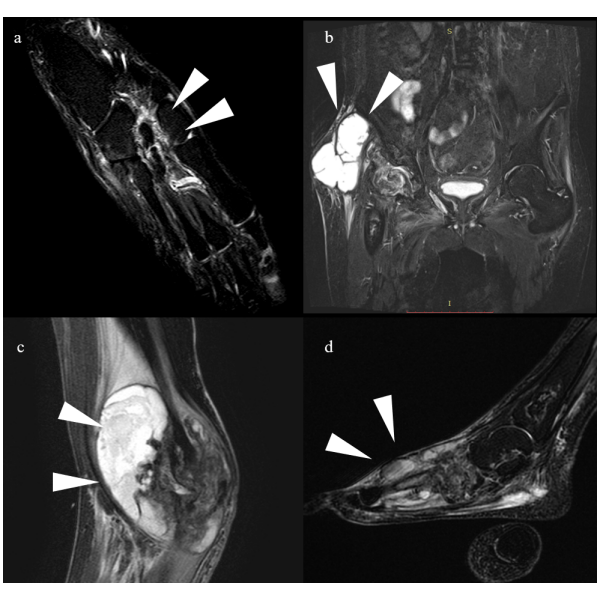
FIGURE LEGEND

Figure 1. Magnetic resonance imaging findings. **a** T2-weighted short-tau inversion recovery (T2w-STIR) imaging revealed high intensity on the navicular articular surface of the talus 3 months after bone marrow transplantation. **b** T2w-STIR revealed unequal high intensity in a multiloculated cyst-like structure around the right hip joint. Osteonecrosis of the right femoral head was also observed. **c** T2w-STIR showed high intensity in multiloculated cysts around the right knee joint. Transformation of the distal end of the humerus was noted. **d** T2w-STIR demonstrated high intensity in the bones of the right foot and cysts in the metatarsophalangeal joint.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