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Original article

Development and exacerbation of pulmonary non-tuberculous mycobacterial infection in patients with systemic autoimmune rheumatic diseases

Sayaka Takenaka[1], Takehisa Ogura[1], Hisaji Oshima[2], Keisuke Izumi[2,3], Ayako Hirata[1], Hideki Ito[1], Kennosuke Mizushina[1], Yuki Inoue[1], Takaharu Katagiri[1], Norihide Hayashi[1] and Hideto Kameda[1]

[1]*Division of Rheumatology, Department of Internal Medicine, Toho University, Tokyo, Japan*

[2]*Department of Connective Tissue Diseases, Tokyo Medical Center, National Hospital Organization, Tokyo, Japan*

[3]*Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*

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Address correspondence to Dr. Hideto Kameda, M.D., Ph.D., Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Toho University (Ohashi Medical Center), 2-22-36 Ohashi, Meguro-ku, Tokyo 153-8515, Japan

E-mail: hideto.kameda@med.toho-u.ac.jp

Abstract

Objectives: To examine the development and exacerbation of pulmonary non-tuberculous mycobacterial (NTM) infection in patients with systemic autoimmune rheumatic diseases (SARD).

Methods: We conducted a case-control study. Seventeen of 7013 patients with SARD fulfilling the criteria for pulmonary NTM infection were enrolled in the NTM group. The control group was matched for age, sex, and SARD at a ratio of 2:1.

Results: Eight patients with rheumatoid arthritis, 4 with systemic vasculitis, 3 with Sjögren's syndrome, and 1 each with dermatomyositis and systemic lupus erythematosus were included in the NTM group. *Mycobacterium avium* was detected in 12 (71%) patients, *M. chelonae* in 2, and *M. intracellulare*, *M. abscessus*, and *M. kansasii* in 1 patient each. Pre-existing lung disease was more common in the NTM group than in the control group (88% versus 38%, p=0.0009), particularly bronchiectasis (65% versus 29%, p=0.033). The body mass index and serum albumin level were significantly lower in the NTM group than in the control group. Six patients (35%) experienced NTM exacerbation during observation. Clinical immune status at the time of NTM diagnosis, as indicated by the peripheral blood leukocyte/lymphocyte count and serum immunoglobulin G level, was unremarkable and comparable between patients with and without exacerbation, as were the treatments for SARD.

Conclusions: In patients with SARD, pulmonary NTM infection may develop and exacerbate without clinically apparent immunosuppression.

Running head: NTM in rheumatic diseases

INTRODUCTION

The advent of immunosuppressive drugs and biological agents has improved the treatment of systemic autoimmune rheumatic diseases (SARD), such as rheumatoid arthritis (RA) and systemic vasculitis. However, these innovations have been accompanied by serious concerns about the risk of opportunistic infections, including pneumocystis pneumonia and mycobacterial infection [1]. For example, the incidence of non-tuberculous mycobacterial (NTM) infection in patients with RA is twice that in the general population, and in the US anti-tumor necrosis factor (TNF) therapy has been reported to increase the incidence of NTM by approximately 5-fold [2]. Japanese post-marketing surveillance of patients with RA receiving biological agents reported that the incidence of NTM infection was 0.1%–0.2%, which is comparable with that of tuberculosis (TB) [3-7]. Further, the incidence of NTM in Nagasaki, Japan, was estimated to be 11.0 and 10.1 per 100,000 in 2008 and 2009, respectively [8], and 14.7 per 100,000 in Japan in 2015 [9], while the national prevalence of NTM in Japan was 33–65/100,000 in 2005 [10].

The 2014 Japanese Respiratory Society guideline on the use of biological agents in NTM [11] states as follows: “In principle, biological agents are contraindicated in patients with NTM disease. However, their use may be considered in cases of NTM caused by *Mycobacterium (M.) avium* complex (MAC), with a number of conditions being met, and in those with high disease activity of RA, but only after fully evaluating the benefit-risk balance”. This statement is based on the fact that, unlike TB, there are no preventive treatments for NTM.

Older age, a longer disease duration, pulmonary comorbidity such as TB, chronic

obstructive pulmonary disease, interstitial lung disease and bronchiectasis, elevated C-reactive protein or erythrocyte sedimentation rate, and treatment with glucocorticoids or biological agents such as anti-TNF, have been identified as risk factors for development and exacerbation of NTM infection in patients with RA or other SARD [12-18]. However, the relative importance of focal (lung disease) and systemic (immune status) factors has not been elucidated to date.

The aim of this case-control study was to identify focal and systemic risk factors for development and exacerbation of NTM infection in patients with SARD. Our observations suggest that pulmonary NTM infection develops and exacerbates without clinically apparent immunosuppression on the basis of pre-existing lung diseases.

PATIENTS AND METHODS

Patients

A total of 5411 patients with SARD visited the Toho University Ohashi Medical Center between April 2003 and March 2013 and 1602 patients visited the Tokyo Medical Center between September 2011 and August 2012. Nineteen (0.4%) of these patients were diagnosed to have NTM infection according to the Japanese Society for Tuberculosis and Japanese Respiratory Society diagnostic criteria [19]. Two patients who were followed up for less than 1 year were excluded, leaving 17 patients eligible for enrolment in the study (Figure 1). Thirty-four patients without mycobacterial infection from Toho University Ohashi Medical Center matched for age, sex, and the diagnosis of SARD were enrolled as control subjects at a ratio of 2:1. Computed tomography (CT) imaging of the chest had been performed as a screening test or for

evaluation of lung disease in all study participants.

Methods

The medical records of the enrolled Japanese patients were retrospectively reviewed. Data on patient demographic and clinical characteristics, as well as disease activity, peripheral blood leukocyte count, lymphocyte count, and serum immunoglobulin G (IgG) levels at the diagnosis of NTM and at the last observation were collected. For patients in the control group, laboratory data were matched for calendar date at the time of the last observation in the NTM group. The findings and interval changes in chest CT throughout the observation period (from the screening or diagnostic images to the last observation) were assessed by agreement between the report by a radiologist and the interpretation by a rheumatologist, and the NTM exacerbation and NTM outcome were judged based on the interval changes in chest images. The binomial activity state of rheumatic diseases, active or inactive, was evaluated based on the principle of the physicians' intention to treat. The study was approved by the institutional ethics committee at Toho University Ohashi Medical Center (approval no. H16050) and that at Tokyo Medical Center (approval no. R16-174). The need for written informed patient consent was waived in view of the retrospective and observational nature of the study.

Statistical analysis

The statistical analysis was performed using JMP Pro (version 11.2, SAS Institute Japan Ltd., Tokyo, Japan). Continuous variables are presented as the median and interquartile range (IQR) and were analyzed using the Mann-Whitney *U* test.

Binomial data were compared between two groups using Fisher's exact test. P-values <0.05 were considered to be statistically significant.

RESULTS

Demographics, clinical features, and outcomes in patients with NTM

The demographic and clinical characteristics of the 17 patients are summarized in Table 1. Eleven (65%) patients were female and the median age at enrollment (last observation) and at the time of diagnosis of NTM was 74 and 68 years, respectively. Eight patients had RA and 3 patients each had microscopic polyangiitis or Sjögren's syndrome. The median duration of rheumatic disease until diagnosis of NTM was 4 years and the median duration of observation after diagnosis was also 4 years. Three patients were noted to have a history of smoking, and 3 and 6 patients, respectively, had malignancy and diabetes (not shown in Table 1).

Fifteen (88%) of the patients who developed NTM had pre-existing lung disease, including bronchiectasis (n=11, 65%), interstitial lung disease (n=4, 24%), and old TB (n=3, 18%). Radiographic cavities were observed in 7 (41%) patients. *Mycobacterium avium* was detected in 12 (71%) patients, *M. chelonae* in 2, and *M. intracellulare*, *M. abscessus*, and *M. kansasii* in 1 patient each. Before the diagnosis of NTM, 11 (65%) patients had been treated with prednisolone (median maximum dose 10 mg/day, range 2–40 mg/day), 6 with methotrexate, 2 patients each with salazosulfapyridine and mizoribine, and 1 patient each with azathioprine, tacrolimus, and infliximab. During management of the underlying SARD and NTM, prednisolone was discontinued in 1 patient and newly added in 2 patients. Methotrexate was continued in 3 patients, and salazosulfapyridine and azathioprine was used in 3 and 2

patients, respectively. Mizoribine, tacrolimus, intravenous cyclophosphamide and golimumab were used in 1 patient each. Thus, the overall treatment of the underlying SARD was not attenuated after diagnosis of NTM, and SARD were inactive in 13 (76%) of the patients at the last observation.

The outcome of NTM was favorable in all patients except for 2, both of whom were female, had bronchiectasis, and had been treated with clarithromycin as monotherapy for MAC infection. Treatment of NTM was initiated in 9 (53%) of the patients (5 with clarithromycin monotherapy and 4 with initial combination chemotherapy). One patient (case 9) received add-on combination chemotherapy after an initial exacerbation of NTM while on clarithromycin monotherapy, which was unsuccessful. It should be noted that the treatment for SARD had not been modified after diagnosis of NTM in the 2 patients with a poor NTM outcome.

Risk factors for development of NTM in patients with SARD

We then compared the demographic and clinical characteristics of NTM patients with those of control patients matched for age, sex, and underlying rheumatic diseases (Table 2). A notable difference between the two group was the presence of pre-existing lung disease (88% versus 38%, p=0.0009), especially bronchiectasis (65% versus 29%, p=0.033). Furthermore, the body mass index and serum albumin level in patients with NTM were significantly lower than the values in the control patients. Peripheral leukocyte and lymphocyte counts and the serum IgG value were comparable between the groups. The treatments for underlying SARD were also similar between the groups. Therefore, it was suggested that the development of pulmonary NTM infection in patients with SARD could be primarily associated with

pulmonary comorbidities leading to pulmonary barrier dysfunction rather than systemic immunosuppression.

Comparison of patients with and without exacerbation of NTM

In addition to the 2 patients with a poor outcome, we identified 4 patients who experienced exacerbation of NTM infection during their clinical course (Table 1). We compared the demographic and clinical characteristics of these 6 patients with those of the patients who did not experience exacerbation of NTM (Table 3). There was no significant difference in age, sex, duration of NTM, type of SARD, radiographic or bacteriologic findings, or type of treatment for SARD between the 2 groups. Combination chemotherapy had been used after exacerbation of NTM in 5 cases (patients 1, 8, 10, and 11 as the initial NTM therapy and patient 9 after worsening while on clarithromycin monotherapy; Table 1). All of these patients (except for patient 9) improved or stabilized on combined therapy. We did not observe any fatal cases of NTM in this study.

NTM infection is regarded as an opportunistic infection, so we also compared the 2 groups for clinical immune status. We observed that clinical immune status at the time of diagnosis of NTM and at the last observation, including peripheral blood leukocyte count, lymphocyte count, and serum IgG level, were within normal ranges and comparable between patients who did and did not experience exacerbations, and even favorable in the former group.

DISCUSSION

Although NTM is known to be an opportunistic infection, pulmonary NTM seems to

develop and progress in patients with SARD despite normal leukocyte and lymphocyte counts and a normal serum IgG level. The results of the present study suggest that pulmonary NTM infection develops and exacerbates without clinically apparent immunosuppression on the basis of pre-existing lung disease in patients with SARD as in those without SARD.

The prevalence of NTM infection was 0.4% in this study, which is higher than the estimated national prevalence of NTM in Japan of 33–65/100,000 [10]. In the US, the incidence rates (per 100,000 person-years) for NTM in the general population, unexposed RA patients, and anti-TNF users were reported to be 4.1 (95% confidence interval [CI] 3.9–4.4), 19.2 (95% CI 14.2–25.0), and 74 (95% CI 37–111), respectively [2].

Among the risk factors for pulmonary NTM infection, pre-existing lung disease, especially bronchiectasis, has been reported to be crucial [20], although bronchiectasis can result from NTM infection [21]. In this study, 65% of the patients who developed NTM had pre-existing bronchiectasis (versus 29% in the control patients, p=0.033), and we were able to obtain chest images even before the diagnosis of pulmonary NTM in patients with SARD (at a median of 2 years previously; Table 1). As shown in this study, bronchiectasis is a pulmonary complication observed in various SARD, including RA and Sjögren's syndrome [22], although it can result from NTM infection [21]. We could not find any characteristics of bronchiectasis in our small group of patients, who had a variety of rheumatic diseases, although a recent report has suggested radiological subgroups [23]. Other risk factors confirmed in this study include a low body mass index [24] and low serum albumin level [25], although these factors were not associated with exacerbation of pulmonary NTM

diseases (Table 3).

Pre-existing lung disease is also a risk factor for a poor outcome in patients with NTM disease [14]. There is a growing body of evidence indicating the importance of host defense mechanisms, such as those provided by the airway epithelial barrier and innate immune cells [26] and/or type 2 cell-mediated immunity [27]. Pulmonary epithelial barrier dysfunction leads to a vicious circle of colonization by pathogens followed by a local inflammatory response and further worsening of pulmonary barrier function.

Unlike in some previous reports [2,13,14, 17], none of our patients died of NTM infection or showed signs of extrapulmonary NTM infection. This finding may be related to the fact that most of our patients had normal peripheral leukocyte and lymphocyte counts, a normal serum IgG level, and well-controlled underlying SARD. Thus, intense immunosuppression can be associated with extrapulmonary dissemination of NTM and a fatal outcome. Two patients' condition (4 and 9 in Table 1) of the 5 who received clarithromycin monotherapy as the initial NTM treatment worsened, while all of the 4 patients who received the initial combination chemotherapy had a favorable outcome. Therefore, our results suggest that initial combination chemotherapy rather than macrolide monotherapy, which is associated with macrolide resistance [28], may be important for a favorable outcome in patients with NTM (predominantly MAC) infection complicated by SARD.

The limitations of this study include the small number of patients with NTM infection, possible selection bias with regard to the controls, the lack of individual or uniform quantifiable activity assessment for SARD, non-availability of lung and immune function data, such as T lymphocyte subsets and interferon gamma/interleukin-12/23

production assays, and the variety of underlying types of SARD. However, the background total of 7013 patients with SARD from two medical centers and the availability of serial chest CT images may be the strengths of this study, although we cannot exclude the possibility that bronchiectasis was caused by preclinical pulmonary NTM in some patients.

In conclusion, bronchiectasis, which could be a manifestation of underlying SARD, was commonly observed in patients with SARD complicated by pulmonary NTM infection. The overall outcome in patients with concomitant SARD and pulmonary NTM infection was fair when adequate combination chemotherapy for NTM infection was provided. Development and exacerbation of pulmonary NTM was not associated with clinically detectable immunosuppression, such as leukopenia, lymphopenia, hypogammaglobulinemia, or the treatment of the underlying SARD.

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CONFLICT OF INTEREST

None

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FIGURE LEGENDS

Figure 1. Flow of participants in this study.

Table 1. Demographic and clinical characteristics of 17 patients with NTM infection and rheumatic diseases

No.	Age (y)	Sex	RD	Lung	Cavity	NTM species	RD before NTM (y)	Initial chest image before NTM (y)	NTM follow-up (y)	Treatment of RD before NTM	Treatment of RD after NTM	RD activity at NTM diagnosis	RD activity at last observation	Initial treatment of NTM	NTM exacerbation	NTM outcome
1	65	F	RA	BE	+	*M. kansasii*	6	9	2	SASP	SASP	Active	Inactive	INH + RFP + EB	+	Improved
2	76	M	RA	BE, ILD	-	*M. absessus*	5	11	1	PSL (5), MTX, MZR	PSL (5), MTX, MZR	Inactive	Inactive	-	-	Stable
3	64	F	SS	BE	-	*M. avium*	5	5	6.5	-	-	Inactive	Inactive	CAM	-	Stable
4	64	F	MPA	BE	-	*M. avium*	2	5	6	PSL (2)	PSL (2)	Inactive	Inactive	CAM	+	Worsened
5	74	F	DM	BE, ILD	-	*M. avium*	0.1	3	7	PSL (40), MTX	PSL (5.5), TAC	Active	Inactive	CAM	-	Stable
6	78	M	MPA	BE, COP	+	*M. intracellulare*	4	0	8	AZA	PSL (5), AZA	Active	Inactive	-	-	Stable
7	80	M	GPA	COPD	-	*M. avium*	0.5	2	2	PSL (10)	PSL (11), AZA	Inactive	Inactive	-	-	Stable
8	82	F	RA	ILD, TB	+	*M. avium*	3	2	2	PSL (10),	PSL (10),	Active	Active	CAM +	+	Stable

										MTX, IFX	SASP			RFP + LVFX		
9	62	F	SS	BE	+	*M. avium*	-5	-5	11	-	-	Inactive	Inactive	CAM	+	Worsened
10	74	M	MPA	BE, ILD	-	*M. avium*	1	1	3	PSL (20)	PSL (60), IVCY	Inactive	Active	RFP + EB + CAM + LVFX	+	Stable
11	57	M	SLE	-	+	*M. avium*	5	0	14	PSL (10), MZR	PSL (3)	Inactive	Inactive	INH + EB + CAM	+	Stable
12	75	F	RA	BE	-	*M. avium*	7	12	3	PSL (2), MTX	-	Inactive	Inactive	-	-	Stable
13	64	F	RA	BE	-	*M. chelonae*	15	12	2	PSL (5)	PSL (6)	Active	Inactive	CAM	-	Stable
14	76	F	RA	BE, TB	-	*M. chelonae*	16	10	4	SASP	SASP, GOL	Active	Inactive	-	-	Stable
15	70	F	RA	-	-	*M. avium*	26	0	6	PSL (5), MTX, TAC	PSL (5), MTX	Inactive	Active	-	-	Stable
16	75	F	RA	TB	+	*M. avium*	0	2	4	MTX	PSL (5), MTX	Inactive	Active	-	-	Stable
17	76	M	SS	Fungal infection	+	*M. avium*	1	1	2	PSL (10)	PSL (10)	Inactive	Inactive	-	-	Stable

PSL (number) indicates prednisolone dose in mg/day. AZA: azathioprine; BE: bronchiectasis; CAM: clarithromycin; COP: cryptogenic organizing pneumonia; COPD: chronic obstructive pulmonary disease; DM: dermatomyositis; EB: ethambutol; F: female; GOL: golimumab; GPA: granulomatosis with polyangiitis; ILD: interstitial lung disease; INH: isoniazid; IVCY: intravenous cyclophosphamide; LVFX: levofloxacin; M: male; MPA: microscopic polyangiitis; MTX:

methotrexate; MZR: mizoribine; NA: not applicable; RA: rheumatoid arthritis; RD: rheumatic disease; RFP: rifampicin; SASP: salazosulfapyridine; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; TAC: tacrolimus; TB: tuberculosis; y: years

Table 2. Comparison of demographic and clinical characteristics between patients with NTM at the diagnosis of NTM and the control patients without NTM

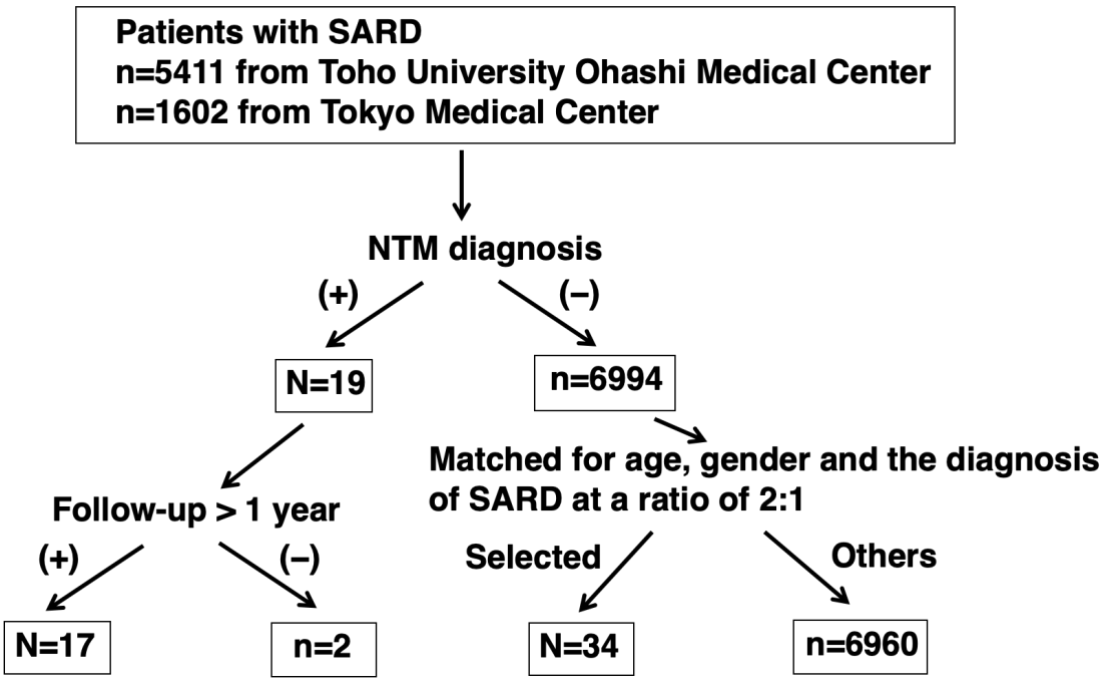
	NTM (n=17)	Control (n=34)	P-value
Age , median (IQR), y	74 (64-76)	74 (68–78)	0.46[a]
Female sex, n (%)	11 (65)	22 (65)	1[b]
Body mass index, median (IQR)	18.3 (16.7–20.2)	21.3(19.3–23.8)	0.0019[a]
RA, n (%)	8 (47)	16 (47)	1[b]
Active rheumatic disease, n (%)	6 (35)	7 (21)	0.31[b]
Pre-existing lung disease, n (%)	15 (88)	13 (38)	0.0009[b]
PSL, n (%)	13 (76)	20 (59)	0.35[b]
Maximum PSL, median (IQR) mg/day	10 (1–40)	4.5 (0–32.5)	0.39[a]
Biological DMARDs, n (%)	2 (12)	7 (21)	0.7 [b]
WBC, median (IQR) $\times 10^3/\mu L$	6.9 (4.6–8.4)	6.0 (4.7–7.4)	0.37[a]
Lymphocyte count, median (IQR) $\times 10^3/\mu L$	1.3 (1.0–1.5)	1.3 (1.0–1.8)	0.55[a]
Serum albumin level (mg/dl) , median (IQR)	3.9 (3.1-4.4)	4.3(4.1-4.75)	0.0074[a]
Serum IgG, median (IQR) $\times 10^3$ mg/dL	1.3 (1.2–1.6)	1.2 (1.0–1.5)	0.39[a]

[a]Mann-Whitney *U* test; [b]Fisher's exact test. DMARDs: disease-modifying antirheumatic drugs; IgG: immunoglobulin G; IQR: interquartile range; PSL: prednisolone; RA: rheumatoid arthritis; WBC: white blood cells.

Table 3. Comparison between patients who did and did not experience exacerbation of NTM infection

	Exacerbation (+) (n=6)	Exacerbation (-) (n=11)	P-value
Age at diagnosis of NTM, median (IQR), y	65 (61–76)	75 (70–76)	0.12[a]
Female sex, n (%)	4 (67)	7 (64)	1[b]
Body mass index , median (IQR)	17.7 (14.95–21.3)	18.7 (17.35–19.75)	0.84[a]
Duration of NTM, median (IQR), y	5 (2–12)	4 (2–7)	0.55[a]
RA, n (%)	2 (33)	6 (55)	0.62[b]
Active rheumatic disease after NTM, n (%)	2 (33)	4 (36)	1[b]
Pre-existing lung disease, n (%)	5 (83)	10 (91)	1[b]
MAC species, n (%)	5 (83)	8 (73)	1[b]
Cavity, n (%)	4 (67)	3 (27)	0.16[b]
PSL, n (%)	5 (83)	8 (73)	1[b]
Maximum PSL, median (IQR) mg/day	11 (4–38)	5 (0–40)	0.61[a]
Biological DMARDs, n (%)	1 (17)	1 (9)	1[b]
NTM treatment, n (%)	6 (100)	3 (27)	0.0090[b]
Monotherapy, n (%)	2 (33)	3 (27)	1[b]
Combination therapy, n (%)	5 (83)	0 (0)	0.0010[b]
Serum albumin level, median (IQR) mg/dl	4.1 (3.2–4.475)	3.7 (3.1–4.4)	0.43[a]
WBC at diagnosis of NTM, median (IQR) $\times 10^3/\mu L$	6.4 (4.3–9.7)	7.0 (4.6–8.3)	0.96[a]
WBC at last observation, median (IQR) $\times 10^3/\mu L$	6.5 (4.5–8.2)	7.1 (5.9–7.6)	1[a]
Lymphocyte count at NTM diagnosis, median (IQR) $\times 10^3/\mu L$	1.5 (1.1–1.9)	1.2 (1.0–1.4)	0.16[a]
Lymphocyte count at last observation, median (IQR) $\times 10^3/\mu L$	1.3 (0.7–1.9)	1.0 (0.9–1.4)	0.31[a]
Serum IgG at NTM diagnosis, median (IQR) $\times 10^3$ mg/dL	1.5 (1.2–2.1)	1.2 (0.98–1.4)	0.14[a]
Serum IgG at last observation, median (IQR) $\times 10^3$ mg/dL	1.6 (1.4–1.9)	1.2 (0.96–1.4)	0.017[a]

[a]Mann-Whitney *U* test; [b]Fisher's exact test. DMARDs: disease-modifying antirheumatic drugs; IgG: immunoglobulin G; IQR: interquartile range; MAC: *Mycobacterium avium* complex; NTM: non-tuberculous mycobacterial infection; PSL: prednisolone; WBC: white blood cells.


Patients with SARD
n=5411 from Toho University Ohashi Medical Center
n=1602 from Tokyo Medical Center
NTM diagnosis
(+)
(–)
N=19
n=6994
Follow-up > 1 year
(+)
(–)
N=17
n=2
Matched for age, gender and the diagnosis of SARD at a ratio of 2:1
Selected
Others
N=34
n=6960