

Clinical characteristics of rheumatoid arthritis patients complicated with pulmonary nontuberculous mycobacterial disease: a cross-sectional case series study

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76

77 **Abstract**

78 **Objectives:** Pulmonary nontuberculous mycobacterial disease (pNTM) is a common pulmonary
79 complication of rheumatoid arthritis (RA), but their association has rarely been researched. We
80 aimed to reveal the clinical characteristics of RA with pNTM.

81 **Methods:** Among all the RA patients who visited Tenri hospital from April 2017 to March
82 2018, we enrolled those fulfilling the 2007 ATS/IDSA diagnostic criteria of pNTM, and sex-
83 and age- matched control group at a ratio of 1:5. Demographic characteristics were compared
84 between the two groups.

85 **Results:** Among 865 RA patients, 35 (4.0%) patients were complicated with pNTM. RA
86 patients with pNTM had significantly lower BMI and significantly higher rheumatoid factor
87 (RF) and anti-citrullinated protein antibody (ACPA) positivity. Bronchiectasis was the most
88 frequent lesion in RA patients with pNTM, followed by clusters of small nodules, patchy
89 consolidation and cavity. Multivariable logistic regression analysis revealed bronchiectasis as a
90 strong independent associated factor of pNTM. Treatment for pNTM was needed in 14 of the 35
91 (40%) RA patients with pNTM and sputum negative conversion was accomplished in 11 of the
92 14 cases (78.6%).

93 **Conclusions:** RA patients with lower BMI, RF/ACPA positivity, and abnormal CT findings
94 including bronchiectasis were associated with pNTM. Treatment for pNTM may attain sputum
95 negative conversion and radiological improvement in patients with RA.
96

97 **Introduction**

98 Rheumatoid arthritis (RA) is a chronic autoimmune disease with synovitis and is often
99 complicated with interstitial lung disease and airway disease. Rheumatoid arthritis patients with
100 lung involvement are at an increased risk of infections because of several factors including lung
101 disease itself, immunosuppressive therapy, and immune dysfunctions related to RA [1–4].

102 Nontuberculous mycobacteria (NTM) are emerging infectious pathogens that infect both
103 immunocompetent and immunocompromised patients and the number of patients is increasing
104 worldwide [5]. This is one of the major causes of chronic lung infection in RA patients and the
105 number of RA patients with pulmonary NTM disease (pNTM) has also increased recently [6]. A
106 recent study has revealed that tumor necrosis factor (TNF) inhibitor use was associated with this
107 increase of pNTM [7]. However, it is still unknown whether the treatment for RA or RA itself is
108 a risk factor for pNTM [8].

109 There have been several studies on RA patients complicated with pNTM [9–18]. These
110 studies focused on the relation of TNF inhibitor use and pNTM, the relative risk of pNTM in
111 RA patients compared to the healthy populations, and the comparison between RA patients with
112 pNTM and those with tuberculosis [9,11–14,16,19]. A few studies focused on the difference
113 between RA patients with pNTM and those without pNTM [15,18] and there were no case

series about RA patients complicated with pNTM.

In this study, we compared RA patients with pNTM and age- and sex-matched RA patients without pNTM in one Japanese referral hospital. We also described a case series of RA patients with pNTM, in order to elucidate the clinical characteristics and courses of these patients.

Materials & Methods

Patients: A total of 865 RA patients who had visited Tenri Hospital, tertiary referral center with 868 beds in Nara, Japan between April 2017 and March 2018 were selected for this study. The RA was diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA [20]. We retrospectively searched the clinical and microbiologic database of the RA patients to identify pNTM according to the 2007 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) NTM diagnostic criteria [21]. Microbiological database since January 2003 was available at our hospital. Thirty-five of the 865 RA patients (4.0%) fulfilled the diagnostic criteria of pNTM, and 175 RA patients without pNTM matched for age and sex were enrolled as control subjects at a ratio of 1:5. Nineteen RA patients who showed NTM positive result only

once in multiple sputum tests were excluded from the control group before age and sex matched control extraction. Rheumatoid arthritis diagnosis and treatment were conducted by rheumatologists and pNTM diagnosis and treatment were conducted by pulmonologists, both at our hospital.

Study design: This was a retrospective cross-sectional study for which clinical data were collected from medical records. Baseline clinical characteristics including age, gender, body mass index (BMI), smoking history, Charlson's comorbidity index (CCI), RA therapy, tender joint counts (TJC), swollen joint counts (SJC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were obtained at the time of data collection between April 2017 and May 2018 [22]. Autoantibody data were collected at the time of RA diagnosis and the highest titer examined till March 2017 was adopted. In our clinical practice, the chest computed tomography (CT) scan was conducted, when lung lesions were suspected in chest X-ray, or when patients started taking methotrexate (MTX) or biological disease-modifying anti-rheumatic drugs (bDMARDs). The chest CT data conducted on the nearest date of data collection was examined for RA patients without pNTM, whereas the examination conducted on the nearest day of pNTM diagnosis was considered for the RA patients with pNTM. The

146 mycobacterial sputum culture was conducted when pNTM was suspected from the patients’
147 symptoms or radiological findings. The bronchoalveolar lavage culture was not routinely
148 assessed and was conducted in two RA patients, who fulfilled the diagnostic criteria of pNTM.
149 Mycobacterial culture tests were performed with standard methods. Samples were incubated for
150 six weeks by an automated liquid method using mycobacteria growth indicator tubes (MGIT™;
151 Nippon Becton Dickinson Company, Ltd., Tokyo, Japan) before 2004 and a BacT/ALERT® 3D
152 system (bioMérieux Inc., Durham, NC, USA) after 2005. If the smear and/or culture for
153 mycobacteria were positive, the sample was subsequently analyzed by polymerase chain
154 reaction (PCR) using a COBAS® AMPLICOR Analyzer (Roche Diagnostics Japan, Tokyo,
155 Japan) before 2017 and TRCReady-80 real-time monitor (Tosoh Co., Tokyo, Japan) thereafter to
156 determine the existence of *M. intracellulare* and *M. avium*. When the species could not be
157 determined by PCR, DNA–DNA hybridization using DDH Mycobacteria® (Kyokuto
158 Pharmaceutical Industrial Co., Ltd., Tokyo, Japan) was conducted before 2016. After 2017, the
159 determination of the species was conducted with the mass spectrometry method using matrix-
160 assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS) using
161 MALDI Biotyper (Bruker Japan, Yokohama, Japan). CCI was scored according to its original

assessment method [22]. The index was scored with comorbidities as follows: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes, hemiplegia or paraplegia, renal disease, malignancy, and HIV/AIDS.

Evaluation of radiological findings: Chest CT scan was assessed by a rheumatologist and a pulmonologist, referring CT analysis reports written by radiologists. Radiological changes during the pNTM follow-up period were assessed using a chest X-ray or chest CT scan.

Data analysis: The demographic characteristics of RA patients with pNTM and those without pNTM were compared. In radiological comparisons, patients who did not undergo a chest CT examination were excluded. Multivariable logistic regression analysis was adopted to estimate odds ratios (OR) and 95% confidence interval (CI) by a forced entry method.

Continuous variables were expressed as mean $\pm$ SD. Categorical variables were reported as numbers and percentages. Univariate analysis was conducted using the chi-squared test or Fisher's exact test appropriately when variates were binary data or categorical data and using Student's *t*-test when variates were numeric. Statistical significance was defined as $p < 0.05$.

Data were analyzed using the Statistical Package for the Social Science (IBM SPSS version

22.0; International Business Machines Corp, New York, USA).

Ethics: This study was conducted after appropriate approval from the institutional ethics committee in accordance with the Declaration of Helsinki.

Results

Clinical characteristics of RA patients with pNTM and without pNTM are described in **Table 1**. RA patients with pNTM had lower BMI ($19.8 \pm 3.8 \text{ kg/m}^2$ vs. $22.4 \pm 4.8 \text{ kg/m}^2$, $p = 0.032$). RA patients with pNTM were significantly less treated with bDMARDs or targeted synthetic DMARDs (b-/ts-DMARDs) (8.6% vs. 28.6%, $p = 0.011$). Autoantibodies including rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positivity were significantly higher in RA patients with pNTM (RF 100% vs. 84.6%, $p = 0.010$ and ACPA 96.6% vs. 79.5%, $p = 0.031$). Inflammatory markers were higher in RA patients with pNTM; CRP (mg/dL) 1.7 ± 1.9 vs. 0.8 ± 1.5 , and ESR (mm/h) 35 ± 28 vs. 25 ± 20 ($p < 0.05$). Although insignificant, TJC and SJC were higher in RA patients with pNTM.

Of the 35 RA with pNTM patients, chest CT scan was conducted in 33 patients, and all the 33 patients had lung lesions. Of the 175 RA without pNTM patients, chest CT scan was conducted in 130 patients. Among the 130 patients, any lesion was not detected in 38 patients

(29.2%) and at least one lung lesion was detected in 92 patients (70.7%). Because the 2007 AST/IDSA NTM diagnostic criteria included abnormal radiological findings, we excluded the 38 RA patients without pNTM who didn't show abnormal CT findings from the analysis to reveal the CT characteristics of RA patients with pNTM in RA patients. The results of the comparison between RA patients with pNTM and those without pNTM were described in **Table 2**. The prevalence of bronchiectasis (BE), cluster of small nodules, consolidation, and cavity were significantly higher in RA patients with pNTM (93.9% vs. 15.2%, 84.9% vs. 22.8%, 63.7% vs. 8.7%, and 30.4% vs. 2.2%, respectively) ($p < 0.05$). Bronchiectasis was found in 45 RA patients and, of those, 31 patients (68.9%) were complicated with pNTM. There was no significant difference in the frequency of ground-glass opacity (GGO), honeycomb, or pleural effusion. Multivariable logistic regression analysis with BMI, RF or ACPA positivity, and bronchiectasis revealed bronchiectasis (Odds ratio 123.2 (95%CI 12.8-1190)) as independent associated factors of pNTM.

Each case description was documented on **Table 3, and 4**. Cases with untreated pNTM were on **Table 3**, with treated pNTM were on **Table 4**. Rheumatoid arthritis was diagnosed before pNTM diagnosis in 33 cases, and the mean duration from RA diagnosis to pNTM

diagnosis was 15.8 ± 11.4 years. In the other two cases, pNTM was diagnosed before RA, and the duration from pNTM diagnosis to RA diagnosis were 3.2 years and 5.3 years. In mycobacterial cultures, *M. avium* was the most frequent species in our cohort (28/35, 80.0%), followed by *M. intracellulare* (8/35, 22.9%), and *M. abscessus* (1/35, 2.9%). One case was infected with plural NTM species. The treatment for pNTM with multiple agents according to ATS/IDSA guideline had been conducted in 14 of the 35 cases (40%) and culture conversion was achieved in 11 of the 14 cases (78.6%), while one case turned out to have *M. abscessus* pulmonary disease after the chemotherapy for *M. avium*.

We also compared RA patients with pNTM who received (14 patients) and did not receive pNTM treatment (21 patients) (**Supplementary Table 1**). Patients who received pNTM treatment were female predominant ($p = 0.03$) and younger ($p = 0.02$). They received more b/ts-DMARDs ($p = 0.03$) and less salazosulfapyridine ($p = 0.002$). Inflammatory markers including CRP and ESR were higher in those who did not receive pNTM treatment ($p = 0.01$). Patients who received pNTM treatment had less cavity ($p = 0.01$) and more cluster of small nodules ($p = 0.04$). Among the 21 RA patients with untreated pNTM, 8 patients exacerbated radiologically, and 13 patients did not show exacerbation (**Table 3**). In exacerbated cases, NB pattern were less

frequent (37.5% vs. 84.6%, $p=0.03$), and male predominant (62.5% vs 7.7%, $p=0.007$). In terms of RA treatment, there were no statistical difference between the two groups.

The b-/ts-DMARDs including tocilizumab, abatacept, and tofacitinib were used in 3 cases after pNTM diagnosis. In the case with tocilizumab and the case with tofacitinib for RA therapy, pNTM was treated with multiple anti-mycobacterial agents successfully (case #33 and case #34, **Table 4**). Tofacitinib was started after the confirmation of negative culture conversion, while tocilizumab was started before receiving pNTM treatment. The case treated with abatacept could not tolerate multiple agents for pNTM, and the therapy for pNTM was discontinued after six months because of a neurologic adverse event (case #35, **Table 4**). In this case, abatacept was tolerated for 2 years with minor radiological deterioration without any antibiotics.

Discussion

Although the number of RA patients with pNTM has been increasing recently, their clinical characteristics, especially treatment outcome, have rarely been reported. This retrospective study investigated the characteristics of RA patients complicated with pNTM. The overall prevalence of pNTM in RA patients was 4.0% (35/865) in our study, and we showed that the macrolide-based 3-drug regimen could be well tolerated in these patients, and resulted in

negative sputum culture conversion in 80% of the patients who received the therapy. We also conducted age- and sex- matched case control study between RA patients with and without pNTM at a ratio of 1:5. The results showed that the ratios of RF positivity and ACPA positivity were significantly higher and BMI significantly lower in RA patients with pNTM than RA patients without pNTM. Regarding RA treatment, b/ts-DMARDs were less frequently used in RA patients with pNTM than those without pNTM in our cohort. Bronchiectasis was the most frequent lesion in RA patients with pNTM, followed by cluster of small nodules, patchy consolidation and cavity. Multivariable logistic regression analysis revealed bronchiectasis as a strong independent associated factor of pNTM.

Previous studies have shown that RA patients with pNTM had lower BMI, lymphocytopenia, higher age, airway disease, longer RA disease duration, and higher disease activity score in 28 joints with erythrocyte sedimentation rate (DAS28ESR), compared with RA patients without pNTM [17,18]. The present study revealed that not only advanced age, lower BMI and inflammatory markers, but also RF and ACPA positivity were more frequent in RA patients with pNTM.

Recently, RF and ACPA positivity has been revealed to be associated with bronchiectasis in RA patients and it is presumed that bronchiectasis is one of the sites of autoimmunity in RA [23–28]. Quirke *et al* reported that bronchiectasis with chronic bacterial infection had higher rate of RF and ACPA positivity, compared to the healthy population [28]. ACPA is an autoantibody against citrullinated peptides and ACPA positivity is associated with RA development and deterioration [29]. The oral pathogens such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are reported to be associated with topical citrullination of peptides (30). Although microorganisms responsible for the citrullination in bronchiectasis are yet unknown, chronic inflammation at RA-associated bronchiectasis may also induce citrullination of peptides and evoke RA development further [31].

Rheumatoid arthritis patients with multiple comorbidities have several risks to use DMARDs and some patients cannot receive optimal RA treatment. According to an observational RA cohort in Japan, RA patients with higher CCI were treated more with prednisolone and less with MTX and bDMARDs [32]. Because preexisting lung lesion is one of the risk factors of MTX-related pneumonitis, the use of MTX may have been avoided [33,34]. TNF inhibitor-related infection risk for NTM has been reported [11,35], and American College

of Rheumatology 2021 guidelines stated TNF inhibitors are associated with increased rates of mycobacterial infection and should be avoided. In our study, RA patients with pNTM were treated less with b-/ts-DMARDs, and the other immunosuppressants, such as MTX, prednisolone (PSL), tacrolimus, or cyclosporin A were comparable between RA patients with pNTM and without pNTM. Only three (8.6%) of RA patients with pNTM were exposed to bDMARDs before pNTM diagnosis (**Table 4**), while the b-/ts-DMARDs were used in 30% of RA patients without pNTM. Although the accurate odds were unclear, rheumatoid arthritis treatment, including b-/ts-DMARDs and other DMARDs, may not be a main factor of pNTM in our RA patients.

The 2007 ATS/IDSA guideline recommended macrolide based 3-drug regimen for *M. avium* complex (MAC) pulmonary disease, although the decision to initiate therapy should be individualized based on a combination of clinical factors including symptoms, progression of the disease, immune suppression, and potential adverse effects [21]. A recent review reported sputum culture conversion rate was 65.7% if treated according to the guideline [36]. In our study, the treatment for pNTM with multiple agents including rifampicin, ethambutol and clarithromycin had been conducted in 14 of the 35 RA with pNTM cases (40%) and culture

conversion was achieved in 11 of the 14 treated cases (78.6%). The treatment outcome was comparable to that in general MAC pulmonary disease patients [36].

Although bDMARDs, including anti-TNF-inhibitors, are known risk factors of pNTM development, whether it can exacerbate pNTM with proper antimycobacterial treatment is still controversial [13]. Multicenter retrospective case series in Japan, involving RA patients with pNTM received bDMARDs and described two cases with continued bDMARDs after the diagnosis of pNTM [37]. One case received etanercept (ETN) without pNTM treatment and showed radiological exacerbation 1 year after ETN administration. The other case was prescribed pNTM treatment, and after the therapy response, tocilizumab was administered. Two years later, the patient's CT findings remained improved. In our case series, two patients received tofacitinib and tocilizumab, with the successful treatment of pNTM and had no radiological exacerbations. One patient received abatacept and showed minor CT exacerbation due to unsuccessful treatment of pNTM, but could tolerate RA treatment with abatacept. *Mycobacterium* species of those 3 cases was *M. avium* and CT patterns were all nodular BE (NB) patterns. These results may suggest that bDMARDs can be used deliberately in RA patients with pNTM; in *M. avium* case, NB CT pattern, and under successful pNTM therapy.

305 The evidence of NTM risk is limited to a small case series of NTM disease in patients treated
306 with biologics other than TNF inhibitors [15]. Further study is required on RA treatment with
307 bDMARDs from larger studies.

308 There are some limitations in this study. First, it was a single-center retrospective study
309 and therefore, selection bias was inevitable. Furthermore, disease activity indices of RA could
310 not be collected, and associations between RA disease activity and risks of pNTM could not be
311 discussed. Second, because this was a cross-sectional study, the assessment of associations
312 between clinical characteristics and pNTM occurrence was limited in accuracy. Our data were
313 regarding the present characteristics of RA with or without pNTM and, therefore, we could not
314 discuss risk factors of RA or pNTM development. Third, in our clinical practice, we did not
315 routinely screen for pNTM. Although negative results for pNTM by sputum culture in
316 patients who showed radiologically possible pNTM had been confirmed, bronchoscopy
317 was not routinely performed. Therefore, accurate number of RA patients with pNTM may be
318 underestimated. For excluding the detection bias, we have tried to exclude 45 RA patients with
319 radiologically possible pNTM (e.g., RA patients with cluster of small nodules and
320 bronchiectasis) from the control group before age and sex matched control extraction. The

results were unchanged except TJC and SJC, which were significantly higher in RA with pNTM patients than RA without pNTM patients. Further studies, including multi-centered and larger size cohort studies, are needed to compare these two groups accurately.

Our study demonstrated that low BMI, RF and ACPA positivity, and CT abnormalities, such as bronchiectasis and clusters of small nodules were associated with pNTM in RA patients. Our case series revealed that treatment for pNTM was needed in 40% of RA patients with pNTM and sputum negative conversion was accomplished in 78.9%. Biological DMARDs might be tolerated in RA patients with conditional clinical backgrounds.

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None.

Conflict of Interest Statement

None.

Table 1. Clinical characteristics of RA patients with and without pNTM at enrollment in this study

	pNTM (n=35)	non-pNTM (n=175)	p value
Sex; male, n (%)	6 (17.2%)	30 (17.1%)	0.999
Age, mean (SD)	71.7 ± 10.8	71.6 ± 10.6	0.974
BMI, mean (SD)	19.8 ± 3.8	22.4 ± 4.8	0.032
Smoking history, n (%)	6 (17.2%)	19 (10.9%)	0.388
Charlson's comorbidity index			
CCI ≥ 3, n (%)	11 (31.5%)	49 (28.0%)	0.553
Present RA treatment			
PSL, n (%)	17 (48.6%)	83 (47.4%)	0.999
MTX, n (%)	17 (48.6%)	115 (65.7%)	0.083
b-/ts-DMARDs, n (%)	3 (8.6%)	50 (28.6%)	0.011
SASP, n (%)	21 (60%)	86 (49.1%)	0.27
BUC, n (%)	11 (31.5%)	42 (24%)	0.395
IGU, n (%)	9 (25.8%)	40 (22.9%)	0.669
Tac, n (%)	8 (22.9%)	23 (13.1%)	0.188
Autoantibodies			
RF, n (%)	35 (100%)	148 (84.6%)	0.010
RF titer (IU/mL), mean (SD)	473 ± 550.7	336.7 ± 509.2	0.162
ACPA ^a , n (%)	28 (96.6%)	116 (79.5%)	0.031
ACPA titer (U/mL), mean (SD)	190.5 ± 178.4	211.5 ± 334.7	0.749
SJC, mean (SD)	1.1 ± 2.1	0.5 ± 1.8	0.067
TJC, mean (SD)	1.6 ± 4.2	0.7 ± 1.8	0.052
CRP (mg/dL), mean (SD)	1.7 ± 1.9	0.8 ± 1.5	0.002
ESR (mm/h), mean (SD)	35 ± 28	25 ± 20	0.018

^a data were unavailable in 35 cases.

340 Abbreviations. ACPA anti-citrullinated protein antibody; bDMARDs biological DMARDs; BMI
341 body mass index; BUC bucillamine; CCI Charlson's comorbidity index; CRP C-reactive protein;
342 ESR erythrocyte sedimentation rate; IGU iguratimod; MTX methotrexate; PSL prednisolone; RA
343 rheumatoid arthritis; RF rheumatoid factor; SASP salazosulfapyridine; SJC swollen joint count;
344 Tac tacrolimus; TJC tender joint count.
345

Table 2. Characteristics of radiological lesions of RA with pNTM and without pNTM in computed tomography at enrollment in this study.

	pNTM (n=33) ^a	non-pNTM (n=92) ^b	p value
GGO	8 (24.2)	38 (41.3)	0.239
Honeycomb	4 (12.1)	6 (6.5)	0.453
Patchy consolidation	21 (63.7)	8 (8.7)	<0.001
Cavity	10 (30.4)	2 (2.2)	<0.001
Nodules	9 (27.3)	50 (54.3)	0.009
Effusion	5 (15.2)	6 (6.5)	0.157
Cluster of small nodules	28 (84.9)	21 (22.8)	<0.001
Bronchiectasis	31 (93.9)	14 (15.2)	<0.001

Abbreviations: GGO ground glass opacities

^a CT scan was not conducted in 2 of 35 RA with pNTM patients.

^b CT scan was not conducted in 45 of 175 RA without pNTM patients mainly because chest X-ray were normal or the patients did not start taking MTX or bDMARDs. Among the 130 patients who conducted CT scan, any lesion was not detected in 38 patients (29.2%) and at least one lung lesion was detected in 92 patients

365 **Table 3.** Case series of RA patients with untreated pNTM.

No	Sex	Age	Preceding Dx	Duration from RA Dx to pNTM Dx (Y)	Duration from pNTM Dx to enrollment (Y)	RA treatment immediately before pNTM ^b Dx	RA treatment at enrollment in this study ^b	Species	CT patterns at the pNTM Dx	Radiological changes
#1	F	79	RA	18.0	1.3	BUC, IGU, SASP, Tac	BUC, IGU, SASP, Tac	<i>M. intracellulare</i>	NB	NC
#2	F	70	RA	15.3	2.0	MTX, PSL (7.5)	MTX, PSL (7.5)	<i>M. avium</i>	NB	NC
#3	M	84	RA	< 1.0	14.3	None	PSL (2.5), SASP	<i>M. avium</i>	NB	NC
#4	F	62	RA	< 1.0	4.6	None	IGU, SASP	<i>M. avium</i>	NB	NC
#5	F	73	RA	9.5	6.8	MTX	MTX	<i>M. avium</i>	NB	NC
#6	F	86	RA	33.2	3.0	PSL (5)	SASP	<i>M. avium</i>	NB	NC
#7	F	70	NTM	-3.2	10.3	None	BUC, MTX, SASP	<i>M. avium</i>	NB	NC
#8	F	71	RA	21.6	4.7	SASP	SASP, Tac	<i>M. avium</i>	Undetermined ^a	NC
#9	F	83	RA	< 1.0	13.8	None	MTX, SASP	<i>M. avium</i>	Undetermined ^a	NC
#10	F	78	RA	< 1.0	0.1	MTX, PSL (15), SASP	MTX, PSL (6), SASP	<i>M. intracellulare</i>	NB	NA
#11	F	80	RA	39.0	0.3	BUC, IGU, PSL (3), SASP	BUC, PSL (5), SASP, IGU,	<i>M. avium</i>	NB	NA
#12	F	69	RA	8.0	0.3	BUC, IGU, MTX, PSL (5), SASP	BUC, IGU, MTX, PSL (2.5), SASP	<i>M. intracellulare</i>	NB	NA
#13	F	56	RA	16.9	0.3	IGU, MTX,	BUC, IGU, MTX,	<i>M. avium</i>	NB	NA

						PSL (5), SASP	PSL (5), SASP			
#14	F	80	RA	< 1.0	2.3	IGU, MTX	IGU, MTX	<i>M. avium</i>	Undetermined ^a	Ex
#15	M	74	RA	< 1.0	2.0	SASP, Tac	SASP, Tac	<i>M. intracellulare</i>	NB	Ex
#16	M	77	RA	< 1.0	1.0	MTX, PSL (10), SASP	PSL (5), SASP	<i>M. intracellulare</i>	Undetermined ^a	Ex
#17	M	75	RA	4.1	8.1	SASP	SASP	<i>M. avium</i>	NB	Ex
#18	M	77	NTM	-5.3	1.0	None	BUC, PSL (10), SASP, Tac,	<i>M. intracellulare</i>	Undetermined ^a	Ex
#19	F	66	RA	< 1.0	7.2	None	BUC, SASP	<i>M. avium</i>	NB	Ex
#20	F	84	RA	32.3	2.0	SASP	BUC, SASP	<i>M. avium</i>	Undetermined ^a	Ex
#21	M	68	RA	25.4	1.8	MTX, PSL (2)	PSL (2)	<i>M. avium</i>	FC	Ex

366 ^a undetermined due to preceding lung diseases, such as massive fibrosis.

367 ^b PSL dose (mg/day) were shown in parenthesis.

368 Abbreviations: BUC bucillamine; Dx diagnosis; Ex exacerbation; F female; FC fibrocavitary pattern; IGU iguratimod; M male; MTX

369 methotrexate; NA not available; NB nodular bronchiectasis pattern; NC no change; PSL prednisolone; SASP salazosulfapyridine; Tac

370 tacrolimus; Y year.

372 **Table 4.** Case series of RA patients with treated pNTM.

No	Sex	Age	Prior Dx	Duration from RA Dx to pNTM Dx (Y)	Duration from pNTM Dx to enrollment (Y)	RA treatment immediately before pNTM Dx	RA treatment at enrollment in this study ^a	Species	pNTM treatment regimen (duration (months))	Sputum conversion	CT pattern of pNTM	Radiological changes
#22	F	75	RA	< 1.0	7.8	Tac	IGU, MTX, Tac PSL (5), SASP	<i>M. avium</i>	RFP, EB, CAM (17)	Negative	NB	NC
#23	F	67	RA	14.6	4.6	BUC, MTX, PSL (10)	IGU, MTX, PSL (12.5), Tac	<i>M. avium</i>	LVFX, EB, CAM (49)	Negative	NB	NC
#24	F	56	RA	15.5	14.8	None	PSL (5), Tac	<i>M. avium</i>	RFP, EB, CAM (17)	Negative	NB	NC
#25	F	46	RA	10.2	13.1	BUC, PSL (5)	BUC, MTX, PSL (5)	<i>M. avium</i>	RFP, EB, CAM (4) (switched due to erythema) ⇒RFP, CAM, LVFX, (117)	Negative	NB	NC
#26	F	71	RA	< 1.0	0.8	MTX	MTX	<i>M. avium</i>	RFP, EB, CAM (21)	Negative	NB	Improved
#27	F	67	RA	< 1.0	2.6	BUC, IGU	BUC, IGU	<i>M. avium</i>	RFP, EB, CAM (24)	Negative	NB	Improved
#28	F	50	RA	25.8	2.4	MTX	MTX	<i>M. avium</i>	RFP, EB, CAM (22)	Negative	NB	Ex

#29	F	69	RA	<1.0	4.0	SASP	SASP	<i>M. intracellulare</i>	RFP, EB, CAM (5) (stopped due to erythema)	Remained Positive	FC	Ex
#30	F	81	RA	< 1.0	12.2	None	BUC, MTX	<i>M. avium</i> <i>M. intracellulare</i> <i>M. abscessus</i>	RFP, EB, CAM (3) (stopped due to patient's request)	MAC ⇔ <i>M. abscessus</i>	NB	Ex
#31	F	41	RA	< 1.0	10.1	BUC, PSL (10)	MTX, PSL (10)	<i>M. avium</i>	RFP, EB, CAM (57)	Negative	NB	Ex
#32	F	68	RA	1.8	3.2	MTX, PSL (4), SASP	MTX, PSL (1), SASP	<i>M. avium</i>	RFP, EB, CAM (20)	Negative	NB	NC
#33	F	69	RA	7.0	3.3	MTX	MTX, TOFA	<i>M. avium</i>	RFP, EB, CAM (18)	Negative	NB	Improved
#34	F	83	RA	< 1.0	6.3	MTX, PSL (7.5)	PSL (3), TCZ	<i>M. avium</i>	RFP, EB, CAM (73)	Negative	NB	NC
#35	F	65	RA	1.5	11.8	MTX	PSL (1), SASP, Tac, ABT	<i>M. avium</i>	RFP, EB, CAM (5) (stopped due to neuropathy)	Remained Positive	NB	Ex

373 ^a PSL dose (mg/day) were shown in parenthesis.

374 Abbreviations: ABT abatacept; CAM clarithromycin; Dx diagnosis; EB ethambutol; Ex exacerbation; F female; M male; MTX methotrexate; NB

375 nodular bronchiectatic pattern; NC no change; PSL prednisolone; RFP rifampicin; SASP salazosulfapyridine; Tac tacrolimus; TCZ tocilizumab;

376 TOFA tofacitinib; Tx treatment; Y year.

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