Mod Rheumatol (2004) 14:143–148
DOI 10.1007/s10165-004-0281-x

ORIGINAL ARTICLE

Yasuhiko Yoshinaga · Tatsuya Kanamori · Yusuke Ota
Tomoko Miyoshi · Hidetoshi Kagawa
Masahiro Yamamura

Clinical characteristics of *Mycobacterium tuberculosis* infection among rheumatoid arthritis patients

Received: July 22, 2003 / Accepted: December 27, 2003

Abstract To evaluate the clinical characteristics of *Mycobacterium tuberculosis* infection in rheumatoid arthritis (RA) patients, we examined the clinical manifestations and radiography/computed tomography (CT) findings in RA patients with tuberculosis (RA+/TB+). A total of 1121 tuberculosis patients were admitted to our hospital from 1995 to 2003, with the RA patients among them comprising 1.8% (20 cases; 9 men and 11 women). This is approximately three times as high as the prevalence of RA in the entire population in Japan. In addition, the RA+/TB+ patients were older and had a longer history of RA than the 140 outpatients in our RA clinic who did not have tuberculosis (RA+/TB−). Half of the RA+/TB+ patients had no symptoms (e.g., cough, sputum, pyrexia), and their tuberculosis was detected accidentally by radiography/CT. The positive rates of the bacilli in the smear and culture of the sputum from the RA+/TB+ patients were lower than those from 143 patients randomly selected from among 1091 tuberculosis patients without any collagen disease including RA (RA−/TB+). The RA+/TB+ patients had a higher incidence of extrapulmonary tuberculosis (30%), including four cases (20%) of miliary tuberculosis, an incidence seven times higher than among the general population of tuberculosis patients. Among 14 cases of pulmonary tuberculosis patients with RA, bilateral lesions and noncavitary lesions were found in 71.4% and 64.3%, respectively, which tended to be a higher incidence than in the RA−/TB+ patients. The mortality rate and sputum conversion time of the RA+/TB+ patients were no different from those of the RA−/TB+ patients. The prevalence of tuberculosis in RA patients is expected to increase after introduction of anticytokine therapy in Japan, and careful observation should be done to avoid this complication in RA patients.

Key words Extrapulmonary tuberculosis · Miliary tuberculosis · *Mycobacterium tuberculosis* · Rheumatoid arthritis (RA)

Introduction

Millions of patients with autoimmune diseases such as rheumatoid arthritis (RA) worldwide are being treated with agents that specifically block the biological activities of interleukin-1 (IL-1) or tumor necrosis factor (TNF) to reduce the severity of their disease. There is a growing body of clinical evidence, however, that neutralization of TNF-α is associated with an increased risk of opportunistic infections, especially *Mycobacterium tuberculosis*.[1] In Japan, anticytokine therapy such as anti-TNF-α antibody has been started. An increased occurrence of tuberculosis is expected after the introduction of anticytokine therapy. The general incidence of tuberculosis in Japan is already fourfold that of the United States.[2] In the present study, we examined the incidence and characteristics of tuberculosis in RA patients who were admitted to our hospital from 1995 to 2003 to evaluate the potential risk of tuberculosis in RA patients.

Patients and methods

A total of 1121 patients with tuberculosis were admitted to our hospital from April 1995 to March 2003; 20 (1.8%) of them had RA as well. There were 9 men and 11 women. Only three (15%) had had a history of tuberculosis, with none of the three under isoniazid prophylaxis.

We evaluated these 20 patients regarding their age, the mean RA duration, the mean RA stage (Steinbrocker), use

Y. Yoshinaga[1] (✉) · T. Kanamori · Y. Ota · H. Kagawa
Department of Rheumatology, National Minami-Okayama Hospital, 4066 Hayashima, Hayashima-cho, Tsukubo-gun, Okayama 701-0304, Japan

T. Miyoshi · M. Yamamura
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan

Present address:
[1]Rheumatic Disease Center, Kurashiki Medical Center, 250 Bakuro-cho, Kurashiki 710-8522, Japan
Tel. +81-86-422-2111; Fax +81-86-422-4150

of disease-modifying antirheumatic drugs (DMARDs) and steroids compared with RA patients without tuberculosis (n = 140) who were controlled in our outpatient clinic during March 2003. To further clarify the clinical characteristics of tuberculosis in RA patients, 143 cases were randomly selected from among 1091 tuberculosis patients without any collagen diseases including RA for comparison with 20 tuberculosis patients who also had RA.

The rheumatoid arthritis was diagnosed by plural rheumatologists according to the revised American College of Rheumatology (ACR) criteria for classification of RA established in 1987. Tuberculosis was diagnosed by detecting *Mycobacterium tuberculosis* in various materials.

The data are presented as the mean ± standard deviation. Student's *t*-test, the chi-square test with Fisher's exact test, and Yates correction were used for statistical analysis. Differences between the mean values with $P < 0.05$ were considered significant. Stat View J – Version 5.0 (Abacus Concepts, Berkeley, CA, USA) was used for the statistical analysis.

Results

Clinical characteristics of RA patients with tuberculosis

The RA patients with tuberculosis (RA+/TB+) were older (71.7 ± 5.7 years) and had a longer history of RA (16.1 ± 13.0 years) than did the outpatients who had RA without tuberculosis (RA+/TB−): 59.8 ± 12.7 years and 9.4 ± 9.1 years, respectively (Table 1). The mean RA stage (Steinbrocker) was slightly higher (3.2 ± 0.8 vs. 2.7 ± 1.1) in the RA+/TB+ patients.

In 14 (70%) of the 20 cases, corticosteroids were used at the time of the tuberculosis diagnosis, which was not different from the RA+/TB− outpatients. However, three (15%) of the RA+/TB+ patients were taking moderate-to-high dosages of steroids (prednisolone >10 mg/day) (Table 2). Moreover, one of them had interstitial pneumonia (prednisolone 60 mg/day) and two had malignant RA (40 and 20 mg/day prednisolone each). DMARDs were used by 45% of the patients (bucillamine in 3 cases, methotrexate in 3 cases, salazosulfapyridine in 1 case, actarit in 1 case, and lobenzarit disodium in 1 case) at the time of the tuberculosis diagnosis.

Symptoms and examination of the sputum from the RA+/TB+ patients

Among the RA+/TB+ patients, here were respiratory symptoms such as expectoration and cough in 9 (45%) and pyrexia in 10 (50%) (Table 3). Symptoms by which the disease might discovered were found in only 11 cases (55%), which was less than that in the tuberculosis patients without RA (RA−/TB+) (80%). The RA+/TB+ patients tended to be asymptomatic, and half of them were diagnosed by chance because of an abnormal shadow on the chest radiograph. The time lag to the diagnosis after the onset (doctor's delay) ranged from 1 to 16 weeks.

Positive findings for the diagnosis of tuberculosis during the sputum examination were found in 9 cases (45%) by the smear and in 14 cases (70%) by DNA examination of *M. tuberculosis* using the polymerase chain reaction (PCR) (Table 3). The PCR results were compatible with the sputum culture results. The rates of finding the bacilli in smears and cultures of sputum from the RA+/TB+ patients were lower than those for the RA−/TB+ patients (45.0% vs. 55.9% and 65.0% vs. 84.9%, respectively).

Clinical characteristics of tuberculosis with RA compared with tuberculosis without RA

Extrapulmonary tuberculosis lesions were observed in six of the RA+/TB+ patients (30%), including four (20%) with miliary tuberculosis (Fig. 1); the other two patients exhibited colon tuberculosis and a retroperitoneal abscess with cellulitis. The frequencies of extrapulmonary tuberculosis and miliary tuberculosis were significantly higher than

Table 1. Comparison between the RA patients with tuberculosis and the general RA patients

Parameter	RA+/TB+ patients (n = 20)	RA+/TB− patients (n = 140)	P
Sex (male:female)	9:11	42:98	NS
Age[a] (years)	71.7 ± 5.7	59.8 ± 12.7	<0.0001
Duration of RA[b] (years)	16.1 ± 13.0	9.4 ± 9.1	<0.01
Stage of RA (Steinbrocker)	3.2 ± 0.8	2.7 ± 1.1	NS
Use of glucocorticoids	14	111	NS
PSL > 10 mg/day	3	2	<0.01
Use of DMARDs	9	117	<0.001
Use of MTX	3	43	NS

[a] Age of RA patients with TB represents age on admission; age of the general RA patients represents age at an outpatient clinic on March 2003

[b] Duration of RA represents the period from the onset of RA to admission of RA patients with TB or on March 2003 in general RA patients

DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; PSL, prednisolone; RA, rheumatoid arthritis; TB, tuberculosis

Table 2. Clinical profiles of tuberculosis patients with RA

Case	Age[a] (years)	Sex	History of TB	Complications	Duration of RA[b] (years)	Stage of RA	Steroid[c] (PSL mg/day)	DMARDs[c]
1	67	F	−	−	30	4	7.5	−
2	69	M	−	Chronic bronchitis	19	4	7.5	BUC
3	65	F	+	Bladder cancer	6	2	4	ACT
4	81	F	−	CRF, DM	11	3	−	−
5	71	M	−	DM	10	4	5	−
6	71	M	−	Gastroduodenal ulcer	21	3	1.6	CCA
7	70	F	−	CRF	9	3	−	−
8	68	F	+	Amyloidosis, CRF	22	3	8	−
9	73	M	−	Malignant RA	3	2	40	MTX
10	74	M	−	Myocardial infarction	12	4	10	MTX
11	79	M	−	Pulmonary emphysema	20	3	−	−
12	64	F	+	Schizophrenia	10	2	−	−
13	77	M	−	Pneumoconiosis, polymyositis[d]	1	2	10	BUC
14	72	M	−	Mitral regurgitation	22	3	2.5	BUC
15	86	F	−	Angina pectoris, chronic hepatitis	1	2	5	SASP
16	67	F	−	Interstitial pneumonia	3	2	60	−
17	74	F	−	Cerebral infarction	20	4	−	−
18	64	F	−	−	12	3	6	MTX
19	71	F	−	Mitral regurgitation	3	2	−	−
20	70	M	−	Malignant RA, angina pectoris	35	4	20	−

[a] Age on admission for tuberculosis
[b] Period from the onset of RA to admission
[c] Daily dosage of steroid; the names of the DMARDs are those that were being taken on admission
[d] This case was reported previously[15]
ACT, actarit; BUC, bucillamine; CCA, lobenzarit disodium; CRF, chronic renal failure; DM, diabetes mellitus; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; PSL, prednisolone; SASP, salazosulfapyridine; TB, tuberculosis

Table 3. Symptoms and sputum examination in the tuberculosis patients with RA

Case	Dx test	Symptoms		Delay of diagnosis (weeks)	Sputum examinations			TB-positive material
		Cough/sputum	Fever		Smear (Gaffky)	TB PCR	Culture (colonies)	
1	Chest X-p	−	+	1	4	+	300	Sputum
2	Symptom	+	+	12	−	+	4	Sputum
3	Symptom	+	+	16	2	+	100	Sputum
4	Chest X-p	−	−	[a]	−	−	−	BALF
5	Chest X-p	−	−	[a]	2	−	−	Sputum
6	Symptom	+	+	1	2	+	10	Sputum
7	Chest X-p	−	−	[a]	−	−	−	Colon biopsy
8	Symptom	−	+	4	−	−	−	Pus from abscess
9	Chest X-p	−	−	[a]	−	+	10	Sputum
10	Chest X-p	−	+	1	−	+	1000	Sputum, pleural effusion
11	Symptom	+	−	1	−	−	−	TBLB
12	Chest X-p	−	−	[a]	−	−	−	Gastric juice
13	Chest X-p	−	−	[a]	−	+	−	Sputum
14	Symptom	+	+	6	−	+	10	Sputum, pleural effusion Vertebral bone
15	Symptom	−	+	10	2	+	50	Sputum, pleural effusion
16	Symptom	+	+	6	9	+	1000	Sputum
17	Symptom	+	+	3	−	+	2	Sputum
18	Symptom	+	−	4	2	+	100	Sputum
19	Chest X-p	−	−	[a]	3	+	20	Sputum
20	Symptom	+	−	10	9	+	1000	Sputum

[a] For subclinical infection, the onset cannot be specified
BALF, bronchoalveolar lavage fluid; Dx, diagnostic; PCR, polymerase chain reaction; TB, tuberculosis; TBLB, transbronchial lung biopsy; X-p, radiograph

among the RA−/TB+ patients (7.0% and 2.8%, respectively) (Table 5).

Among the RA+/TB+ patients, pulmonary tuberculosis was observed in 14 (70%), 9 (64.3%) of whom had noncavitary lesions and 10 (71.4%) of whom had bilateral pulmonary lesions (Fig. 2). The frequencies of noncavitary lesions and bilateral spread of pulmonary lesions were higher than those in the RA−/TB+ patients, but there were no significant differences. Tuberculous pleuritis was associated with the pulmonary lesions in five patients, two of whom also had tuberculous spondylitis (Table 4).

Table 4. Type of tuberculosis, therapy, and outcome in patients with RA

Case	Pulmonary lesions	Extrapulmonary lesions	Therapy	Outcome	Sputum conversion time (months)
1	–	Miliary tuberculosis	HRE	Improved	3
2	b III 2	–	HRE	Improved	1
3	b III 2	–	HRE	Improved	3
4	r III 2	Tuberculous pleuritis	HR	Improved	1
5	r II 1	Tuberculous pleuritis	HRSE	Improved	1
6	b II 2	–	HRSE	Improved	1
7	–	Colon tuberculosis	HRE	Improved	[a]
8	–	Retroperitoneal abscess, cellulitis	RS	Died of renal failure	[a]
9	b III 2	–	HRE	Improved	3
10	–	Miliary tuberculosis Tuberculous pleuritis	HES	Improved	1
11	r II 1	–	HR	Improved	[a]
12	r III 1	–	HRE	Improved	[a]
13	b III 2	–	HRE	Improved	1
14	b III 2	Tuberculous pleuritis, tuberculous spondylitis	HRSE	Improved	2
15	b III 2	Tuberculous pleuritis, tuberculous spondylitis	HEL	Improved	4
16	b II 3	–	HRS	Died of respiratory failure	3
17	–	Miliary tuberculosis, lymphadenitis	HRE	Improved	1
18	b III 2	–	HRE	Improved	2
19	–	Miliary tuberculosis	HRE	Improved	1
20	b II 2	–	HRE	Died of cerebral infarction	3

[a] No germs were detected on admission

E, ethambutol; H, isoniazid; L, levofloxacin; R, rifampicin; S, streptomycin

Pulmonary lesions are described according to the classification of the Japanese Society for Tuberculosis: b, bilateral; r, right; l, left; II, noncavitary lesions; III, cavitary lesions; 1–3, spreading of the lesions: 1, less than one-third of the hemilung; 3, more than hemilung

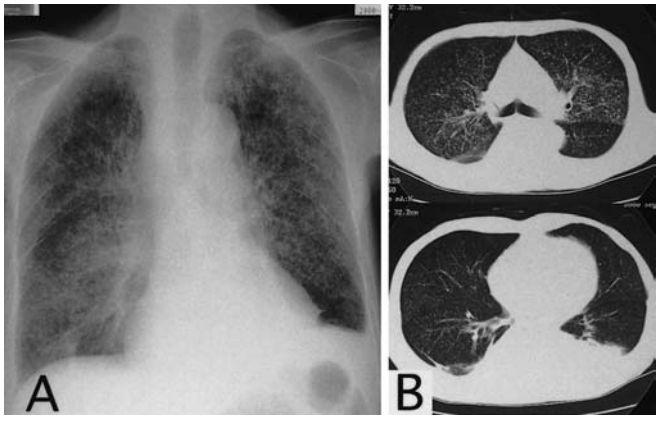

Fig. 1. Chest radiograph (**A**) and computed tomography (CT) scans (**B**) of case 10. Diffuse micronodular lesions spread in both lungs, which are typical findings of miliary tuberculosis. Of our 20 tuberculosis patients with rheumatoid arthritis (RA), 4 (20%) had miliary tuberculosis

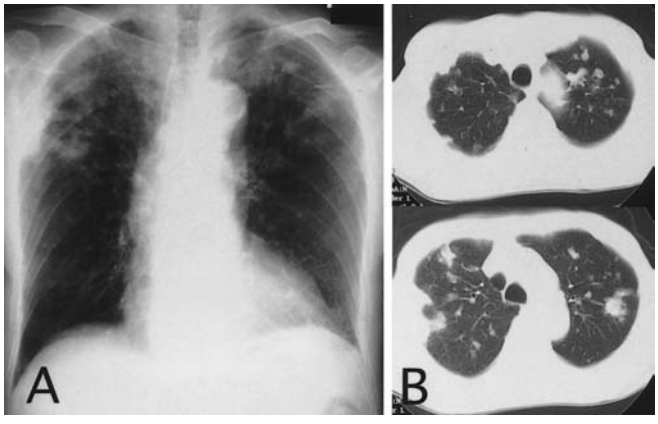

Fig. 2. Chest radiograph and CT scans of case 9. The infiltrative shadows spread to the upper lobes of both lungs without cavitary lesions. Of 14 pulmonary tuberculosis patients with RA, 10 (71.4%) had bilateral lesions and 9 (64.3%) had noncavitary lesions

Of the 20 RA+/TB+ patients, 3 (15%) died of the following causes: renal failure due to amyloidosis, respiratory failure due to progression of interstitial pneumonia, and complications of cerebral infarction (1 case each), although tuberculosis was not the direct cause of death. In the other 17 patients, the bacilli were eradicated after 1–4 months (mean 1.8 ± 1.2 months) of treatment. The mortality rate (14%) and the sputum conversion time (mean 1.7 ± 1.3 months) of the RA+/TB+ patients were similar to those of the RA−/TB+ patients (Table 5).

Discussion

It has been reported that the incidence of tuberculosis in patients with collagen diseases such as systemic lupus erythematosus (SLE) is high owing to the prolonged use of moderate to high dosages of corticosteroids.[3,4] The clinical characteristics of tuberculosis in the SLE patients were reported as follows: (1) a higher incidence rate; (2) more frequent extrapulmonary involvement; (3) more extensive pulmonary involvement; and (4) a higher relapse rate than

Table 5. Comparison between the RA patients with TB and the general TB patients

Parameter	RA+/TB+ patients (n = 20)	RA−/TB+ patients (n = 143)	P
Sex (male:female)	9:11	101:42	<0.05
Age[a] (years)	71.7 ± 5.7	64.3 ± 19.6	NS
Smear positive	9	80	NS
Culture positive	13	121	<0.05
Pulmonary TB	14	133	<0.005
Noncavitary lesions	9	68	NS
Bilateral lesions	10	61	NS
Extrapulmonary TB	6	10	<0.005
Miliary TB	4	4	<0.01
Sputum conversion time (months)	2.0 ± 1.2	1.8 ± 1.2	NS
Death	3	20	NS
Death from TB	0	12	NS

[a] Age at the time of admission for tuberculosis

with RA.[5] The present study demonstrated that the number of RA patients among all tuberculosis patients was approximately three times as high as the prevalence of RA in the entire population in Japan.[6] Moreover, the frequencies of noncavitary pulmonary lesions and bilateral pulmonary lesions were higher, and extrapulmonary lesions (especially miliary tuberculosis) were more frequent in the RA patients than in the general tuberculosis population, suggesting a higher risk for severe tuberculosis than expected. It is possible that RA masked the symptoms and may be responsible for the increased frequency of severe tuberculosis.

The male/female ratio of RA patients complicated with tuberculosis was 9:11. Considering that the ratio of RA patients in Japan is 1:3 to 1:4,[6] the incidence of tuberculosis with RA in the men could be higher than that in the women. The RA+/TB+ patients were older than the RA+/TB− group, and the duration of the RA was longer with a more advanced RA stage than in the RA+/TB− outpatients.

The use of corticosteroids in the RA+/TB+ patients was not different from that in the RA+/TB− patients. However, the percentage of RA+/TB+ patients receiving moderate to high dosage of corticosteroid (prednisolone at >10 mg/day) was higher than that for the RA+/TB− patients. Taking moderate to high doses of corticosteroid for a long time could be responsible for the bilateral pulmonary lesions and extrapulmonary lesions, especially with miliary tuberculosis.[7,8] It was reported that the relative risk of infection in patients treated with corticosteroids was 1.6, although the risk of infection was less if the patients received 10 mg/day or if the cumulative steroid dose was less than 700 mg,[9] suggesting that corticosteroid use should be carefully matched to the patient's needs, and the amount of drug used should be kept to the minimum dosage necessary.

In contrast, DMARDs were used at the time the tuberculosis was detected, but there was no difference between the modality of the DMARDs and the type of tuberculosis. These results are in agreement with those of a previous study showing that the risk of infection in patients with RA who take methotrexate appears to be small.[10] Further studies are needed to clarify the relation between tuberculosis and immunosuppressive medication in the RA patients.

Recent studies suggest that patients with chronic inflammatory diseases benefit from anticytokine therapy. However, there is a growing body of clinical evidence that neutralization of TNF-α is associated with an increased risk of opportunistic infections, including mycobacterial diseases.[1,11] Keane et al. reported 70 cases of tuberculosis among 147 000 patients with RA or Crohn's disease who had received infliximab, a humanized anti-TNFα monoclonal antibody, within 12 weeks; 40 (57.1%) of these patients exhibited extrapulmonary tuberculosis.[12] Moreover, it was reported that during treatment with anti-TNFα antibodies there is often destabilization of the granulomas or failure to form an organized granuloma.[13] Consequently, there is an increase in the bacterial burden in various tissues. A Spanish group reported that the calculated risk ratio of tuberculosis in patients treated with anti-TNFα antibodies was 90.1-fold compared with that for the general population in Spain, and it was 19.9-fold compared with that of the general RA patient population.[14] In Japan, anticytokine therapy, such as with anti-TNFα antibody, also has been started. Considering that the incidence of tuberculosis in Japan is more than four times higher than that in the United States,[2] careful observation is essential to avoid the complication of tuberculosis in RA patients.

Acknowledgments We are grateful to Dr. Atsuhiko Tada (Department of Internal Medicine, National Minami-Okayama Hospital), Dr. Noriko Kanzaki (Department of Radiology, National Minami-Okayama Hospital), and Dr. Toshihiro Takao (Department of Endocrinology, Metabolism, and Nephrology, Kochi Medical School) for their invaluable comments and suggestions.

References

1. Dinarello CA. Anti-cytokine therapeutics and infections. Vaccine 2003;21:S24–S34.
2. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. JAMA 1999;282:677–86.
3. Kim HA, Yoo CD, Baek HJ, Lee EB, Ahn C, Han JS, et al. *Mycobacterium tuberculosis* infection in a corticosteroid-treated

rheumatic disease patient population. Clin Exp Rheumatol 1998; 16:9–13.
4. Sasaki Y, Yamagishi F, Yagi T, Yamatani H, Kuroda F, Shoda H. A clinical study in the collagen disease patients who developed pulmonary tuberculosis during cortico-steroid administration. Kekkaku 2000;75:569–73.
5. Yun JE, Lee SW, Kim TH, Jun JB, Jung S, Bae SC, et al. The incidence and clinical characteristics of *Mycobacterium tuberculosis* infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol 2002;20: 127–32.
6. Shichikawa K, Inoue K, Hirota S, Maeda A, Ota H, Kimura M, et al. Changes in the incidence and prevalence of rheumatoid arthritis in Kamitonda, Wakayama, Japan, 1965–1996. Ann Rheum Dis 1999;58:751–6.
7. Muto S, Sakurai N, Yamamoto K, Nishiyama H, Kurasawa T, Kawai M, et al. A clinical study on pulmonary tuberculosis developed in association with corticosteroid treatment. Kekkaku 1985;60:421–8.
8. Kobashi Y, Yoneyama H, Okimoto N, Matsushima T, Soejima R. Clinical analysis of pulmonary tuberculosis in association with corticosteroid therapy. Kekkaku 1999;74:789–95.
9. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989;11:954–63.
10. Cunnane G, Doran M, Bresnihan B. Infections and biological therapy in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:345–63.
11. Mohan AK, Cote TR, Siegel JN, Braun MM. Infectious complications of biologic treatments of rheumatoid arthritis. Curr Opin Rheumatol 2003;15:179–84.
12. Keane J, Gershon S, Weise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agents. N Engl J Med 2001;345:1098–104.
13. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of TNF in the development of bactericidal granulomas during BCG infection. Cell 1989;56:731–40.
14. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003;48:2122–7.
15. Miyoshi T, Yoshinaga Y, Ota Y. Two cases of rheumatoid arthritis developed after polymyositis. Ryumachi 2003;43:583–90.