—Case Reports—

Active Tuberculosis in a Patient Receiving Adalimumab for Psoriatic Arthritis and Chemoprophylaxis for Latent Tuberculosis Infection

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Tumor necrosis factor (TNF) inhibitors, including adalimumab, are widely used to treat refractory psoriatic arthritis (PsA). Although isoniazid chemoprophylaxis is generally effective in preventing reactivation of latent tuberculosis infection (LTBI), prophylactic measures do not fully protect against development of active tuberculosis. We report a rare case of active tuberculosis despite chemoprophylaxis for LTBI in a patient receiving adalimumab for PsA. A 60-year-old Japanese woman who had received a diagnosis of psoriasis at age 35 years presented with arthralgia of the right hand, which she first noticed 2 months previously. Physical examination showed scattered erythematous papules and plaques with scales on her trunk, extremities, and scalp. Her right metacarpophalangeal and proximal interphalangeal joints were swollen and painful, and her right wrist and elbow were painful. PsA was diagnosed and adalimumab was initiated. Because an interferon-γ release assay (IGRA) showed a borderline result at screening, isoniazid was administered as chemoprophylaxis for LTBI. At 22 months after initiation of adalimumab, IGRA was positive and chest CT disclosed centrilobular nodules in both lungs and swelling of multiple lymph nodes. Culture of sputum at 24 months demonstrated *Mycobacterium tuberculosis*. Active tuberculosis was diagnosed, and treatment with a combination of isoniazid, rifampicin, ethambutol hydrochloride, and pyrazinamide was started. To ensure timely diagnosis and treatment of active tuberculosis, a tuberculosis expert should be consulted at an early stage, with regular screening and monitoring. (J Nippon Med Sch 2023; 90: 480–485)

Key words: active tuberculosis, adalimumab, chemoprophylaxis, latent tuberculosis infection, psoriatic arthritis

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease associated with psoriasis[1] and is diagnosed in accordance with the classification criteria for PsA[2]. Biologics have been available for treatment of patients with refractory psoriasis, including PsA, since 2010 in Japan[3], and tumor necrosis factor (TNF) inhibitors, including adalimumab, are widely used to treat refractory PsA[4]. However, biologics, especially TNF inhibitors, may reactivate latent tuberculosis infection (LTBI). The Biologics Review Committee of the Japanese Dermatological Association for Psoriasis recommends blood examination for interferon (IFN)-γ release assays (IGRAs), including the T-SPOT.*TB* test (Oxford Immunotec Ltd., Abingdon, UK), together with chest imaging before and after initiation of biologics at screening and monitoring[3]. In T-SPOT.*TB*-positive patients, oral isoniazid (INH) 300 mg/day should be prophylactically administered, usually for 6 months, starting from 3 weeks before initiation of biologics. In patients with diabetes and those suspected of being immunocompromised, INH should be administrated for 9 months[3]. INH chemoprophylaxis is generally effec-

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Table 1 Serial T-SPOT.*TB* results

After ADA therapy (months)	Results	Negative control	A antigen (ESAT-6)	B antigen (CFP10)	Positive control
0	Borderline	0	6	1	80
1	Negative	0	4	3	395
3	Negative	0	2	1	136
6	Positive	0	15	2	234
11	Borderline	0	6	3	318
17	Negative	0	0	0	83
22	Positive	0	11	5	132
40	Negative	0	0	3	115
46	Negative	0	0	0	193

ADA, adalimumab; ESAT, early secretary antigenic target; CFP, culture filtrate protein

tive for prevention of reactivation of LTBI[5], but prophylactic measures do not fully prevent development of active tuberculosis[6,7]. Herein, we report a rare case of active tuberculosis in a patient with PsA receiving adalimumab despite chemoprophylaxis for LTBI.

Case Report

A 60-year-old Japanese woman who had received a diagnosis of psoriasis at age 35 years was treated with topical corticosteroids and vitamin D_3, with limited effect, at a nearby clinic. She became aware of arthralgia of the right hand 2 months earlier and was referred to us in September 2018. She consented to the submission of this case report for publication. She had no apparent history of tuberculosis or contact with tuberculosis patients and had received the Bacille de Calmette et Guérin (BCG) vaccine. Physical examination revealed scattered erythematous papules and plaques with scales on her trunk, extremities, and scalp. The psoriasis area and severity index (PASI) score was 4.8. Her nails were intact. Her right metacarpophalangeal and proximal interphalangeal joints of the middle finger were swollen and painful, and her right wrist and elbow were painful. On laboratory examination, C-reactive protein (CRP) was 0.23 mg/dL (normal, ≤0.14 mg/dL) and T-SPOT.*TB* was borderline (6 counts, normal, ≤4 counts, **Table 1**). Chest computed tomography (CT) disclosed no signs of tuberculosis, pneumonia, or interstitial pneumonia. PsA was diagnosed and adalimumab was initiated because of severe arthralgia. The initial dose was 80 mg, followed by 40 mg/dose, at 2-week intervals[3]. Three months after adalimumab treatment, the dose was increased to 80 mg because of the inadequate response. One year after adalimumab treatment, the PASI score was 0 and PsA arthralgia had resolved (CRP 0.03 mg/dL).

Table 1 and **Figure 1** show the serial T-SPOT.*TB* results and the timeline of her clinical course, respectively. The T-SPOT.*TB* test was performed according to the manufacturer's instructions at SRL, Inc. (Shinjuku, Tokyo)[8]. In brief, sensitized T lymphocytes were detected by capturing secreted IFN-γ after *in vitro* stimulation with the tuberculosis antigens early secretory antigenic target (ESAT) 6 and culture filtrate protein (CFP) 10. On the basis of the number of spots produced, T-SPOT.*TB* results are reported as positive, negative, invalid, or borderline[8]. A positive result was defined as a spot count of ≥8 induced by either tuberculosis antigen after subtracting the negative control. A negative result was defined as a spot count of ≤4 induced by both tuberculosis antigens after subtracting the negative control[8]. Because T-SPOT.*TB* showed a borderline result at screening, INH 300 mg/day was administered as chemoprophylaxis for LTBI for 6 months (**Table 1** and **Fig. 1**). Because T-SPOT.*TB* was positive at 6 months after initiation of adalimumab, INH was readministered for another 9 months (from 8 to 17 months) as chemoprophylaxis (**Fig. 1**). From 19 months after initiation of adalimumab, the patient sometimes coughed but had no fever. At 22 months, T-SPOT.*TB* was positive again and chest CT disclosed centrilobular nodules in both lungs and swelling of lymph nodes in the supraclavicular fossa and paratracheal lymph nodes.

A tuberculosis expert suspected granulomatous diseases such as disseminated tuberculosis and sarcoidosis. The serum level of angiotensin-converting enzyme was 34.7 U/L (normal, ≤25.0 U/L). Chest CT showed that a paratracheal lymph node was larger than before the initiation of adalimumab (**Fig. 2a and b**). Transbronchial needle aspiration of the enlarged lymph node with en-

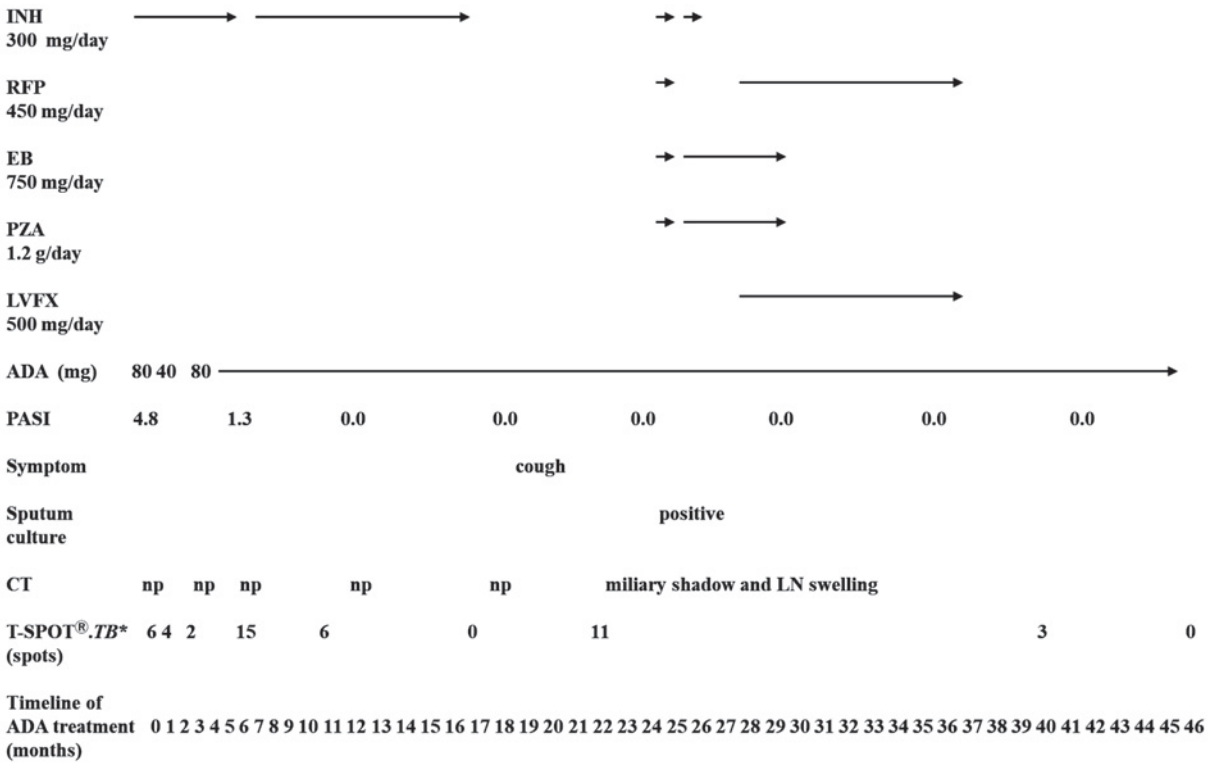

Fig. 1 Timeline of clinical course.
INH, isoniazid; REP, rifampicin; EB, ethambutol hydrochloride; PZA, pyrazinamide; LVFX, levofloxacin hydrate; ADA, adalimumab; PASI, psoriasis area and severity index; CT, computed tomography; np, nothing in particular; * T-SPOT®. *TB* shows the maximum spot number induced by tuberculosis antigens, after subtracting the negative control.

dobronchial ultrasound disclosed a few granulomatous lesions with necrosis, but did not demonstrate *Mycobacterium tuberculosis* on acid-fast bacilli (AFB) culture or polymerase chain reaction. Culture of sputum at 24 months after the initiation of adalimumab, but not at 22 months and 23 months, demonstrated *M. tuberculosis* by the antigen test and mass spectrometry, although the AFB smear of the sputum was negative. The identified *M. tuberculosis* was not resistant to INH. Active tuberculosis was diagnosed, and treatment for tuberculosis with a combination of INH 300 mg/day, rifampicin (REF) 450 mg/day, ethambutol hydrochloride (EB) 750 mg/day, and pyrazinamide (PZA) 1.2 g/day was started at 25 months (**Fig. 1**). After consulting the tuberculosis expert, adalimumab was continued, taking care to prevent immune reconstitution inflammatory syndrome. Because of liver dysfunction and general fatigue, the treatment regimen for tuberculosis was adjusted (**Fig. 1**). From 28 months, levofloxacin hydrate (LVFX) was administered with EB, PZA, and REF. From 30 months, REF and LVFX were administered for 7 months (**Fig. 1**). Chest high-resolution CT at 26 months disclosed centrilobular nodules in both lungs (**Fig. 2c**), and these signs were mitigated at 37 months (**Fig. 2d**). At 40 and 46 months, T-SPOT.*TB* was negative (**Table 1** and **Fig. 1**). Ten months after the completion of treatment, tuberculosis had not recurred.

Discussion

Although rare, active tuberculosis has been reported in psoriasis patients treated with TNF inhibitors in Japan, which has a moderate tuberculosis burden[9,10]. TNF-γ is a cytokine that is important in the containment of *M. tuberculosis* in macrophages[10]. In post-marketing surveillance of the TNF inhibitor infliximab, active tuberculosis was found in 14 of 5,000 (0.3%) registered patients with rheumatoid arthritis in Japan[5]. Extrapulmonary tuberculosis was found in 7 cases (50.0%). Eleven cases developed in the first 2,000 patients, and only 3 cases developed in the latter 3,000 patients. The frequency of prophylactic treatment for tuberculosis increased in the latter group[5], indicating that INH chemoprophylaxis is effective for the prevention of reactivation of LTBI. A post hoc case-control study of 7,755 patients with rheumatoid arthritis treated with adalimumab in Japan found that 22 patients (0.3%) developed active tuberculosis[11]. Despite the high frequency of extrapulmonary tuberculosis (17/22, 77.3%), all 22 tuberculosis patients had pulmonary signs and symptoms. In our patient, CT images suggested lung and

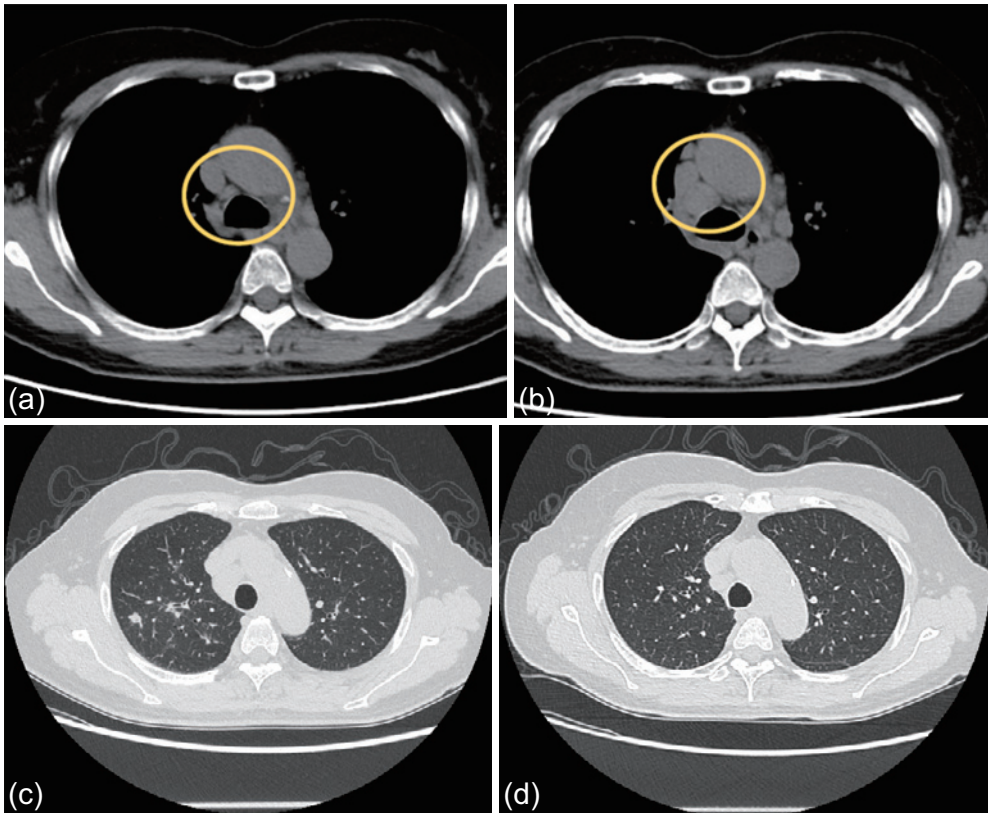

Fig. 2 (a, b) Chest CT revealed enlargement of a paratracheal lymph node (b: circle) after initiation of adalimumab (a: circle). (c) Chest high-resolution CT at 26 months disclosed centrilobular nodules in both lungs. (d) Chest high-resolution CT at 37 months showed mitigation of the signs shown in (c).

lymph node involvement with tuberculosis. Of the patients who received prophylaxis, none developed active tuberculosis after treatment with adalimumab[11]. A large-scale prospective post-marketing surveillance study of the safety of infliximab in 764 Japanese psoriasis patients (average duration of observation, 183 days) observed no active tuberculosis[12]. A 24-week post-marketing study of the safety of adalimumab in 731 Japanese psoriasis patients found that 1 patient (1/731, 0.1%) had pulmonary tuberculosis during the study[13]. Prophylactic administration of INH was performed but adherence was low. In a French nationwide retrospective study of psoriasis patients treated with TNF inhibitors, 8 centers reported 12 cases tuberculosis between 2006 and 2014[6]. All patients had adequate screening for LTBI. Seven, 4, and 1 patient were treated with infliximab, adalimumab, and certolizumab, respectively. This study showed that tuberculosis could still develop despite adherence to tuberculosis prevention guidelines and that prophylactic measures did not fully prevent development of tuberculosis[6].

T-SPOT.*TB* is one of the IGRAs and a useful method for LTBI diagnosis in patients with psoriasis[14]. It has high sensitivity and specificity but cannot distinguish between active tuberculosis and LTBI. The usefulness of T-SPOT.*TB* for diagnosis of tuberculosis was compared with that of the tuberculin skin test (TST)[15]. T-SPOT.*TB* detected 70 of 72 cases of tuberculosis, indicating a sensitivity of 97.2%. TST results were available for 45 of these patients. Only 40 (89%) of these 45 patients were positive on TST, as compared with all 45 (100%) in the T-SPOT.*TB*[15]. Furthermore, TST is more likely to be positive in BCG-vaccinated persons than in unvaccinated persons, whereas T-SPOT.*TB* results are not associated with BCG vaccination[16]. In our patient, serial T-SPOT.*TB* results were obtained after adalimumab therapy, chemoprophylaxis for LTBI, and combination therapy for active tuberculosis (**Table 1** and **Fig. 1**).

One reason why chemoprophylaxis for LTBI could not prevent the occurrence of tuberculosis in our case is that we started adalimumab at the same time as chemoprophylaxis, not at 3 weeks before initiation. We decided to start adalimumab soon because of her severe arthralgia. Another reason is that we initially administered INH for 6 months, not 9 months, although we readministered it

for another 9 months after discontinuation for 2 months. INH is metabolized to *N*-acetyl INH by hepatic *N*-acetyltransferase 2 (NAT2), and patients with tuberculosis are classified as rapid, intermediate, and slow acetylators in accordance with polymorphisms of the *NAT2* gene[17]. The efficacy of INH is limited in rapid acetylators because the plasma concentration of INH is low[18]. Although we did not evaluate polymorphisms of the *NAT2* gene in our patient, we cannot rule out the possibility that she was a rapid acetylator and that INH was not effective for her, in light of the fact that about half of Japanese people are rapid acetylators.

We were able to continue adalimumab treatment for PsA during tuberculosis treatment, which helped maintain our patient's quality of life. Generally, biologics are discontinued after a diagnosis of tuberculosis and are restarted after completion of treatment for tuberculosis[18]. However, the present tuberculosis expert thought that it would be possible to continue biologics during tuberculosis treatment if 3 conditions were met, namely, (i) AFB smear-negative sputum, (ii) absence of comorbidities such as diabetes, and no drugs that suppress the immune system such as systemic corticosteroids or anticancer drugs, (iii) high adherence to anti-tuberculosis treatment. Because these 3 conditions were met in our patient, we continued adalimumab treatment.

We were able to diagnose and treat active tuberculosis at an early stage before the discharge of *M. tuberculosis* with regular screening and monitoring by IGRA and chest CT in this case. About half of tuberculosis cases induced by treatment with biologics are extrapulmonary tuberculosis, and IGRA is potentially valuable for diagnosis of active extrapulmonary tuberculosis in lymphadenopathy[19]. It is essential to consult a tuberculosis expert at an early stage with regular screening and monitoring, to ensure timely diagnosis and treatment of active tuberculosis, especially in countries with a moderate or severe tuberculosis burden, such as Japan.

In summary, we reported a rare case of active tuberculosis despite chemoprophylaxis for LTBI in a patient receiving adalimumab for PsA. We were able to diagnose and treat active tuberculosis at an early stage with regular screening and monitoring and to continue adalimumab treatment for PsA during tuberculosis treatment. The ineffectiveness of chemoprophylaxis for LTBI in our case might have been due to the late introduction and short period of initial chemoprophylaxis. To ensure timely diagnosis and treatment of active tuberculosis, a tuberculosis expert should be consulted at an early stage.

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References

1. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology (Oxford). 2020 Mar;59 (Suppl 1):i37–46.
2. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665–73.
3. Saeki H, Terui T, Morita A, et al. Japanese guidance for use of biologics for psoriasis (the 2019 version). J Dermatol. 2020 Mar;47(3):201–22.
4. Ozaki S, Ichiyama S, Ito M, Hoashi T, Kanda N, Saeki H. Real-world blood examination screening data before initiation of biologics for psoriasis patients. J Dermatol. 2022 May;49(5):534–8. Epub 2022 Feb 22.
5. Takeuchi T, Tatsuki Y, Nogami Y, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):189–94.
6. Guinard E, Bulai Livideanu C, Barthelemy H, et al. Active tuberculosis in psoriasis patients treated with TNF antagonists: a French nationwide retrospective study. J Eur Acad Dermatol Venereol. 2016 Aug;30(8):1336–41. Epub 2016 Jun 3.
7. Oh JH, Ham SP, Park HJ. Disseminated tuberculosis in a psoriasis patient under adalimumab treatment despite the chemoprophylaxis of latent tuberculosis: a case report. Ann Dermatol. 2021 Feb;33(1):77–81. Epub 2020 Dec 30.
8. Rego K, Pereira K, MacDougall J, Cruikshank W. Utility of the T-SPOT®.TB test's borderline category to increase test resolution for results around the cut-off point. Tuberculosis (Edinb). 2018 Jan;108:178–85. Epub 2017 Dec 18.
9. Koga M, Terawaki S, Tatsukawa R, Fujita M, Imafuku S, Nakayama J. Development of miliary tuberculosis related to anti-tumor necrosis factor-alpha inhibitor therapy for pustular psoriasis. J Dermatol. 2013 Jun;40(6):476–7. Epub 2013 Mar 21.
10. Kaneko S, Tsuruta N, Yamaguchi K, et al. Mycobacterium tuberculosis infection in psoriatic patients treated with biologics: real-world data from 18 Japanese facilities. J Dermatol. 2020 Feb;47(2):128–32. Epub 2019 Nov 24.
11. Watanabe A, Matsumoto T, Igari H, Sawa J, Yamaguchi Y, Sakatani M. Risk of developing active tuberculosis in rheumatoid arthritis patients on adalimumab in Japan. Int J Tuberc Lung Dis. 2016 Jan;20(1):101–8.
12. Torii H, Terui T, Matsukawa M, et al. Safety profiles and efficacy of infliximab therapy in Japanese patients with plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic erythroderma: results from the prospective post-marketing surveillance. J Dermatol. 2016 Jul;43(7):767–78. Epub 2015 Dec 24.
13. Asahina A, Torii H, Ohtsuki M, et al. Safety and efficacy of adalimumab treatment in Japanese patients with psoriasis: results of SALSA study. J Dermatol. 2016 Nov;43 (11):1257–66. Epub 2016 Apr 30.
14. Latorre I, Carrascosa JM, Vilavella M, et al. Diagnosis of tuberculosis infection by interferon-gamma release assays in patients with psoriasis. J Infect. 2014 Dec;69(6):600–6. Epub 2014 Aug 19.
15. Meier T, Eulenbruch HP, Wrighton-Smith P, Enders G,

Regnath T. Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice. Eur J Clin Microbiol Infect Dis. 2005 Aug;24(8):529–36.
16. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet. 2003 Apr;361(9364):1168–73.
17. Mushiroda T, Yanai H, Yoshiyama T, et al. Development of a prediction system for anti-tuberculosis drug-induced liver injury in Japanese patients. Hum Genome Var. 2016 Jun;3:16014.
18. Matsumoto T. [Impact of tuberculosis caused by anti-TNF-alpha agents in Japan, problems with many phases]. Rinsho Rheumati. 2006 Mar;18(1):24–35. Japanese.
19. Shin JA, Chang YS, Kim HJ, Ahn CM, Byun MK. Diagnostic utility of interferon-gamma release assay in extrapulmonary tuberculosis. Diagn Microbiol Infect Dis. 2015 May;82(1):44–8. Epub 2015 Feb 14.

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