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A Patient with Urinary Tract Tuberculosis During Treatment with Etanercept

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient: Female, 58
Final Diagnosis: —
Symptoms: —
Medication: —
Clinical Procedure: —
Specialty: —

Objective: Diagnostic/therapeutic accidents

Background: Tumor necrosis factor (TNF)-α inhibitors are widely used for rheumatoid arthritis (RA). However, there are several risks to use TNFα inhibitors. Given the properties of TNF-α inhibitors, prevention and early detection of tuberculosis (TB) are especially important. Even among TNF-α inhibitors, the risk of TB infection differs according to each drug. The incidence of TB is lowest with etanercept (ETN). We present a case of urinary tract TB during treatment with ETN.

Case Report: A 58-year-old woman was receiving ETN for RA. Before starting ETN, isoniazid (INH) prophylaxis was started. RA was well controlled by ETN. However, 32 months after starting ETN, she noticed urinary frequency and a sensation of residual urine. The diagnosis was elusive, and it took 3 months until urinary tract TB was finally diagnosed. The TB resolved with antituberculosis medication, but RA disease activity flared up after ETN was discontinued. ETN was resumed with careful monitoring for TB recurrence. After resuming ETN, the RA was again well controlled, with no recurrence of TB.

Conclusions: Patients should be monitored for development of TB during ETN treatment, but ETN can be used safely with careful management.

MeSH Keywords: Arthritis, Rheumatoid • Tuberculosis, Urogenital • Tumor Necrosis Factor-alpha

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/893416

Background

The treatment of rheumatoid arthritis (RA) has changed dramatically. With early aggressive treatment, joint destruction can be prevented and the long-term prognosis may be improved. With the advent of biologic drugs, even patients who were previously refractory to treatment may now experience a marked decrease in RA activity. However, because tumor necrosis factor (TNF) -α is a cytokine involved in cellular immunity, careful monitoring for possible infection is necessary. Given the properties of TNF inhibitors, prevention and early detection of tuberculosis (TB) are especially important. A medical history of TB, a chest X-ray, and interferon-gamma assay are important to take account of the prophylaxis use of anti-TB drug, isoniazid (INH) before giving TNF inhibitors.

Case Report

We present a case of a 58-year-old woman with RA. In 1999, the patient received the diagnosis of RA with symptoms of polyarthritis at the age of 49 years. She had diabetes and hypertension. Methotrexate (MTX) was started in 2005, and the dose was increased to 8 mg/week, but her RA activity did not decrease. Her disease classification was stage III class 2. The addition of ETN was considered in March 2006, and tests were performed beforehand. Routine blood test results were normal except for an elevated HbA1c of 6.9%. Table 1 shows the blood test results and changes in DAS28-4/CRP. A chest X-ray and electrocardiogram showed no abnormalities.

The patient denied having had previous TB or contact with a TB patient, but a tuberculin skin test was weakly positive (erythema: 55×36 mm, no induration).

INH prophylaxis was started 1 month before ETN. INH 200 mg/day (4.6 mg/kg) was given for 9 months. When ETN was added to the treatment regimen, the RA disease activity decreased gradually. Three months after starting ETN, the patient was switched to self-injections. The dose of prednisolone (2.5 mg/day) was gradually decreased and discontinued after 6 months of ETN. After 21 months of ETN, the dose of MTX was decreased to 6 mg/week. At first, the dose of ETN was 25 mg/week. After 27 months of ETN, the dose of ETN was increased to 50 mg/week. About 1 month after the ETN dose was increased, the patient experienced generalized malaise on the day of ETN injection. There were no objective signs such as fever, and the generalized malaise resolved by the next day. After 29 months of ETN, the dose of ETN was decreased to 25 mg/week.

After 32 months of ETN, the patient developed urinary frequency and a sensation of residual urine. The ETN was stopped, and she was evaluated by a local urologist. She was diagnosed with cystitis, and antibiotics were prescribed. After starting the antibiotics, the frequent urination did not improve, and the patient continued to void every few hours.

About 3 months after the frequent urination started (after 35 months of ETN), the patient was evaluated by the Department of Urology at Fukuoka University Hospital. A urinalysis revealed sterile pyuria, so cytology and acid-fast bacilli (AFB) cultures

Table 1. Blood test results and DAS28-4/CRP.

	Before treatment	8 weeks after ETN started	When INH discontinued	When ETN discontinued	When ETN resumed	8 weeks after ETN resumed
RBC (/μL)	447	454	468	395	434	429
WBC (/μL)	9170	5640	6360	7530	8810	6500
PLT (×10⁴/μL)	27.6	21.1	22.2	17.9	22.9	19.2
AST (U/L)	14	30	43	52	21	69
ALT (U/L)	15	53	63	63	35	115
ALP (U/L)	324	329	418	254	312	223
γ-GTP (U/L)	21	52	54	78	33	75
LDH (U/L)	199	188	198	198	226	201
CRP (mg/dL)	1.06	0.13	0.19	0.23	2.59	0.45
HbA1c (%)	6.9	7.1	7	6.2	6.3	–
DAS28-4/CRP	3.74	1.33	1.94	2.09	6.16	1.41

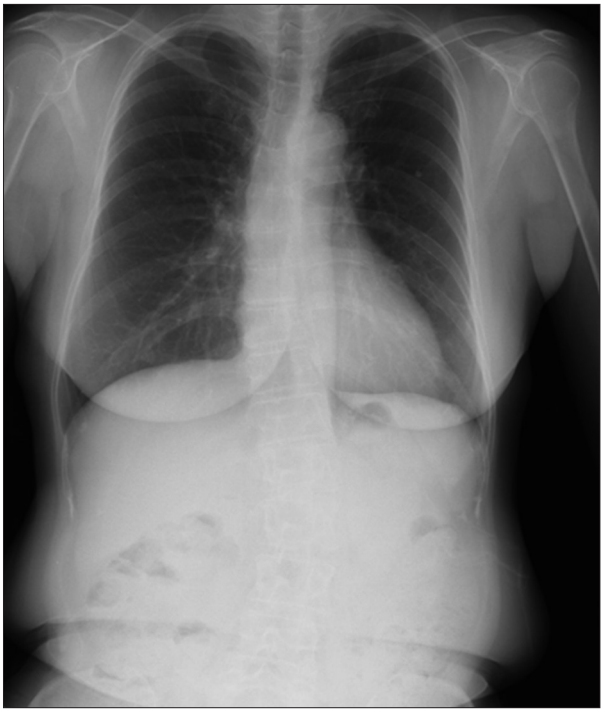

Figure 1. Chest X-ray.

were obtained. The results of cytology were Papanicolaou class II, and the results of AFB smears were Gaffky 2. TB infection was strongly suspected, so without waiting for the results of PCR, oral 4-drug anti-TB therapy (INH, pyrazinamide, ethambutol, and rifampicin) was started. The PCR results for urinary *Mycobacterium tuberculosis* were later found to be positive.

A chest X-ray and chest CT scan showed no abnormalities in the lung fields (Figure 1). Sputum AFB smears and cultures were also negative, and pulmonary TB was ruled out. Abdominal CT of the left kidney showed dilation of the calyces of the upper and lower poles and thinning of the parenchyma (Figure 2). There was mildly increased fat tissue density near the ureteropelvic junction, and in the late phase, contrast excretion from the left kidney was decreased. The left ureteral wall was thickened, with narrowing of the ureteropelvic junction. There was bladder mucosal enhancement and wall thickening. Based on the results of abdominal CT, renal TB with spread of inflammation to the ureter and bladder was suspected. There was no outflow obstruction due to narrowing of the urinary tract on an intravenous pyelogram (IVP) (Figure 3). Urinary tract TB was diagnosed based on these findings.

The patient received oral 4-drug anti-TB therapy (INH, pyrazinamide, ethambutol, and rifampicin) for 4 months and 3 drugs orally (INH, ethambutol, and rifampicin) for another 4 months. The symptoms of cystitis improved, and after anti-TB therapy was discontinued, there was no recurrence. Urinary tract culture results were negative for 2 consecutive months

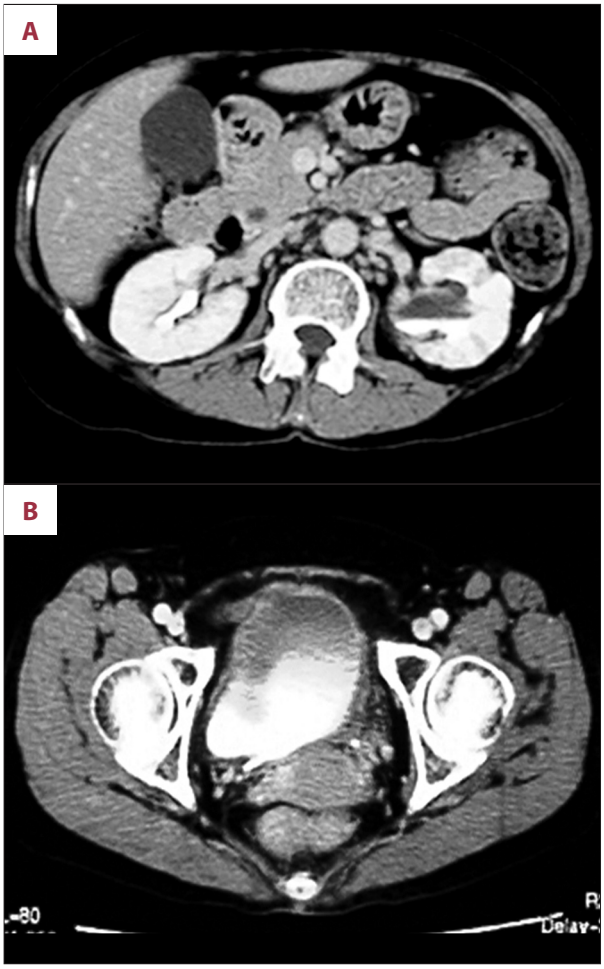

Figure 2. Abdominal CT scan. (**A**) Dilated calyces of the left kidney and decreased contrast excretion. Enlargement of left para-aortic lymph nodes. (**B**) Bladder mucosal enhancement and wall-thickening.

after anti-TB therapy was discontinued, and the treatment of TB was complete.

After ETN was discontinued, the patient continued receiving MTX 4 mg/week and oral celecoxib 200 mg/day for treatment of RA, but disease activity was difficult to control, so resumption of ETN was considered. About 6 months after TB treatment was completed, the results of an interferon-gamma assay (QuantiFERON®TB second generation) were 0.2 IU/mL. At 50 months after ETN was initially started, INH 300 mg/day was started for prophylaxis. At 51 months after ETN was initially started, ETN was resumed. After oral INH was restarted, mild liver dysfunction was noted, but these were improved with ursodeoxycholic acid. At 69 months after ETN was initially started, the oral INH was discontinued after consultation with a pulmonologist, nephrologist, and urologist. Since INH has been discontinued, there has been no TB recurrence. Figure 4 shows the clinical course of this patient.

Discussion

ETN inhibits TNFα activity, and even in patients with MTX-resistant RA, has an excellent effect on reducing RA disease activity. However, because TNFα is a cytokine involved in cellular immunity, careful monitoring for possible infection is necessary. Given the properties of TNF inhibitors, prevention and early detection of TB are especially important.

TNFα plays a central role in the attack of *M. tuberculosis* bacilli by macrophages and in granuloma formation. Therefore, there is a markedly increased risk for development of TB during TNF inhibitor treatment [1,2]. Extrapulmonary TB usually accounts for a small percentage of TB infections, but during TNF inhibitor treatment, more than half of TB infections are due to extrapulmonary TB [2–4]. However, most patients with extrapulmonary TB during TNF inhibitor treatment have disseminated TB; to date, urinary tract TB has only been reported in 1 patient being treated with the TNF inhibitor infliximab [2].

Even among TNF inhibitors, the risk of TB infection differs according to each drug. In studies in England and France comparing 3 TNF inhibitors – ETN, infliximab (IFX), and adalimumab (ADA) – the incidence of TB was lowest with ETN [3,4]. In studies in Japan, the incidence of TB during ETN treatment was only about 1/3 that with IFX [5,6]. One of the reasons for differences in the risk of infection due to these different drugs is differences in their mechanism of action. The TNF receptor drug (ETN), in the absence of rheumatoid factor, will itself not induce apoptosis of TNF-expressing cells. Therefore, compared to the TNF antibody drugs (IFX and ADA), because of weaker inhibition of granuloma formation, the risk of TB infection is lower with ETN [7].

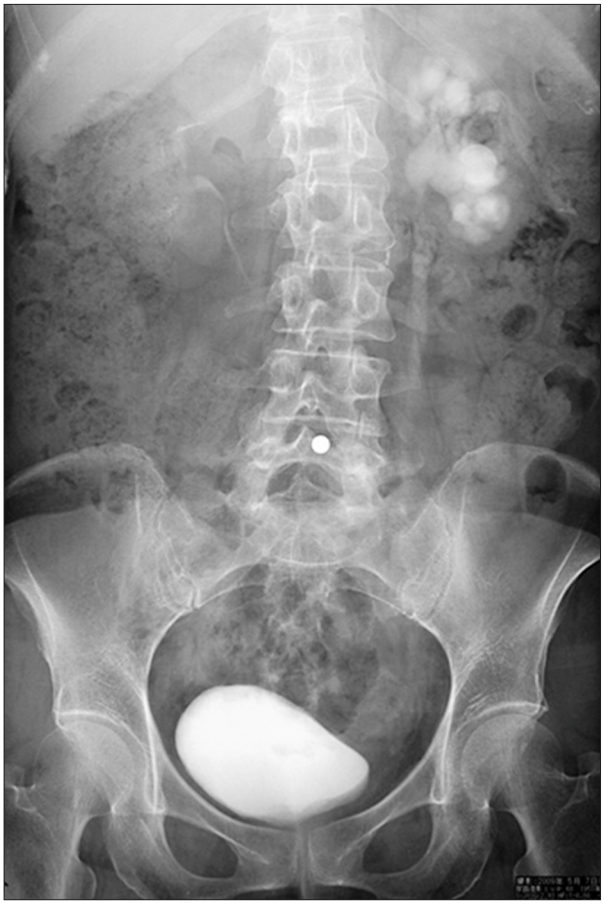

Figure 3. Intravenous pyelogram (IVP). Hydronephrosis and ureteral dilation. No outflow obstruction due to urinary tract narrowing.

Among the TNF inhibitor drugs, although the risk of TB infection during ETN treatment is relatively low, these infections may be more severe if they do develop, so precautionary measures

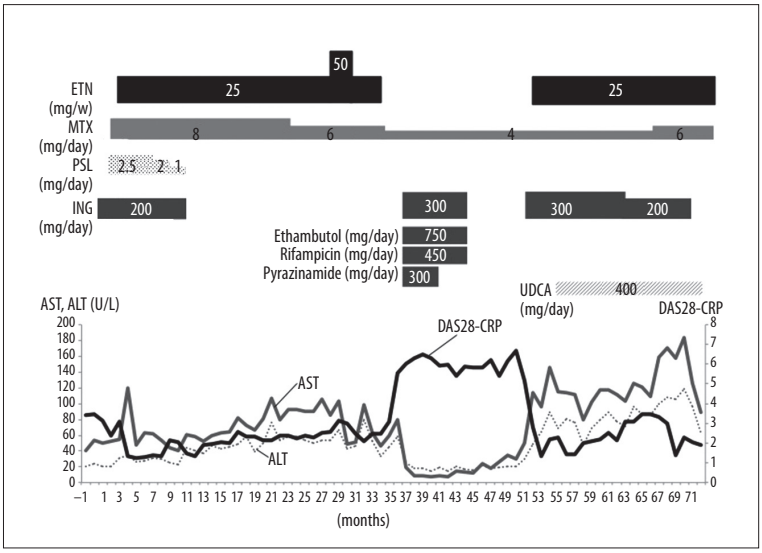

Figure 4. Clinical course of the patient. Before starting ETN, INH prophylaxis was started. RA was well controlled by ETN. At 32 months after starting ETN, urinary tract TB occurred, and ETN was stopped. The TB resolved with antituberculosis medication, but RA disease activity flared-up after ETN was discontinued. ETN was resumed after 51 months. After resuming ETN, the RA was again well controlled, without TB. ETN; etanercept, MTX; methotrexate, PSL; prednisolone, INH; isoniazid, UDCA; ursodeoxycholic acid, AST; aspartate aminotransferase, ALT; alanine aminotransferase, DAS; disease activity score, CRP; c-reactive protein.

are necessary. In particular, screening for latent TB infection is essential before starting ETN. Screening usually consists of a medical history, family history (determining whether any family members have TB), imaging studies, and a tuberculin skin test. The tuberculin skin test is easy, but false-negative and false-positive results are a problematic issue. False negatives may occur in RA patients who are taking steroids or immunosuppressant drugs, and with aging, negative conversion is more likely. TB infection has been reported in 3.4% of patients who have a negative tuberculin test [8]. In addition, in populations in which the majority of persons are vaccinated with BCG, and in populations where exposure to atypical mycobacteria is not uncommon, false-positive rates for tuberculin tests are high [9]. Therefore, this makes screening difficult with tuberculin skin tests in Japan.

The tuberculin skin test has been used to diagnose TB infection, but more recently, a blood interferon-gamma assay (QuantiFERON®TB second generation) has been developed, which is very useful for TB diagnosis and is not affected by BCG vaccination [11]. The present patient was initially evaluated for possible latent TB using the tuberculin skin test alone, but additional testing with an interferon-gamma assay (QuantiFERON®TB second generation) might have been useful. Currently, all patients with a positive tuberculin test at our hospital have additional testing with an interferon-gamma assay (QuantiFERON®TB second generation), and since the present patient, we have not encountered TB infection during use of a TNF inhibitor.

The present patient had a chest X-ray before starting ETN that showed no abnormalities, and there was no prior history of TB or contact with another person who had TB. However, the tuberculin skin test was weakly positive. In such cases with latent TB infection, the risk of recurrence is high with ETN, and INH prophylaxis was given.

The Japan College of Rheumatology issued "Guidelines for TNF inhibitors in rheumatoid arthritis," and prophylaxis with INH 300 mg/day for 6–9 months was generally recommended. However, until revisions in 2008, there was no mention about doses in lower body weight patients. Therefore, in the present patient with a small body habitus, and who had a history of drug-related liver dysfunction with another medication, it was decided to use INH at a dose of 200 mg/day. Gómez-Reino et al. recommended that, in patients with a suspected prior history of TB infection based overall from the medical history, tuberculin skin test, and imaging findings, INH 5 mg/kg (maximum 300 mg) should be given orally for at least 1 month prior to starting a TNF inhibitor. In such patients who received INH as prophylaxis for a total of 9 months, they reported no occurrence of TB [10]. In the present patient, TB infection may have occurred because the 4.6 mg /kg dose of INH might have been too low, with an insufficient prophylactic effect.

Urinary tract TB results from hematogenous spread of TB to the kidneys and further spread to the ureters and bladder. Many patients are asymptomatic while the TB lesions are limited to the kidneys. When these lesions spread to the bladder, symptoms such as urinary frequency, dysuria, and a sensation of residual urine develop, which are difficult to distinguish from nonspecific cystitis, and hematuria and cloudy urine develop [12]. The present patient had urinary frequency and a sensation of residual urine, but a decrease in the percentage of patients presenting with typical cystitis symptoms has recently been reported, so caution is necessary [12]. A definitive diagnosis of TB requires identification of *M. tuberculosis* in a specimen or biopsy tissue, and thus considerable time may be required until diagnosis. Therefore, anti-TB therapy, as in the present patient, is started without waiting for a confirmatory diagnosis. The present patient finally had 2 consecutive culture results that were negative, and treatment for TB was completed after 8 months.

In patients with a clear history of TB infection, ETN should ideally not be given. However, the present patient had poor control of RA disease activity after ETN was discontinued, and resumption of ETN had to be considered. Despite the history of TB, we thought that ETN would be safe provided that there was no latent TB infection. Thus, we performed the interferon-gamma assay (QuantiFERON®TB second generation), in which ≥0.35 IU/mL is positive, with ≤0.1 IU/mL negative. The result was 0.2 IU/mL in the present patient, so latent TB could again not be ruled out. We considered the risk of TB recurrence when ETN was resumed, so we decided to administer anti-TB prophylaxis. The dose of INH was increased to 300 mg/day in an effort to more reliably prevent TB, but after resuming INH, liver dysfunction occurred gradually.

When abnormal liver function becomes a problem during INH treatment, rifampicin can also be used for prophylaxis. However, this patient also had diabetes, and to avoid increased glucose levels, the patient was not switched to rifampicin. INH was continued with the addition of ursodeoxycholic acid. The currently recommended period of prophylaxis is 6–9 months. However, given the development of TB during ETN treatment in the present patient, and the fact that even after 8 months of anti-TB therapy, the interferon-gamma assay (QuantiFERON®TB second generation) had not converted to negative, we carefully considered when to discontinue prophylactic therapy. Using a multidisciplinary approach, specialists in urology, pulmonology, gastroenterology, and nephrology were consulted, and a decision was made to discontinue INH at 68 months after ETN had initially been started (18 months after ETN resumption). Since INH was discontinued, there has been no TB recurrence.

Conclusions

In conclusion, ETN is a very effective drug, but because of its mechanism of action, the risk of infection must always be considered. In particular, because the incidence of TB is higher in Japan than in other developed countries, TB must always be considered in patients with infections that are difficult to diagnose. Urinary tract TB, as in the present patient, although rare, should also be kept in mind.

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Conflict of interest

None.

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