Severe bacterial sepsis results in delayed diagnosis of tuberculous lymphadenitis in a rheumatoid arthritis patient treated with adalimumab

Soichiro Sawamura, Takamitsu Makino*, Takamitsu Johno, Junji Yamashita, Daisuke Niimori, Satoshi Fukushima, Hironobu Ihn

Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan.

Summary

Although tumor necrosis factor (TNF)-α inhibitors are effective in patients with rheumatoid arthritis (RA), an increased risk of infections often becomes a serious problem. It is well known that TNF-α inhibitors increase the risk of tuberculosis, but extrapulmonary tuberculosis often induced by them is difficult to diagnose using routine imaging examinations. We described a case of delayed diagnosis of a tuberculous lymphadenitis in a patient with RA treated with TNF-α inhibitor because of the complications of severe bacterial sepsis. In this case, rescreening with the interferon-γ release assay and excisional biopsy were useful in confirming the diagnosis of extrapulmonary tuberculosis. In the case we presented, she had other risk factors, that is, advanced age at the start of anti-TNF-α treatment or concomitant use of corticosteroid, might contribute to the development of complex infections. We should keep in mind that careful follow-up and appropriate examinations are necessary in caring for patients administering immunosuppressive treatments including anti-TNF-α drugs.

Keywords: Tumor necrosis factor-α, septic shock, extrapulmonary tuberculosis, interferon-γ release assay

1. Introduction

Recently, the treatment for rheumatoid arthritis (RA) has changed drastically. Notably, biological drugs inhibiting tumor necrosis factor (TNF)-α have beneficial effects in patients with RA who are refractory to the conventional anti-rheumatoid therapy including disease-modifying antirheumatic drugs (DMARDs) (1). However, infections are the most common and important adverse effects of TNF-α inhibitors, because TNF-α is a key cytokine involved in cellular immunity (2). Especially, TNF-α plays an important role in host defense against Mycobacterium tuberculosis by mediating granuloma homeostasis and containment of latent disease (3). Therefore, prevention and early detection of tuberculosis (TB) are very important in patients with RA treated with TNF-α inhibitors (4). In this manuscript, we described a case of delayed diagnosis of a tuberculous lymphadenitis in a patient with RA treated with TNF-α inhibitor because of the complications of severe bacterial sepsis and septic shock.

2. Case Report

The patient was a 70-year-old woman who was diagnosed as having RA with polyarthritis at the age of 67 years. She underwent treatment with non-steroid anti-inflammatory drugs and sulfasalazine (up to 2,000 mg/day) for 1 year and then the treatment was changed to bucillamine (up to 300 mg/day) and prednisolone (5 mg/day). Methotrexate (MTX) was not prescribed because of deterioration of renal function. She had...
also systemic sclerosis for 7 years and was visiting our hospital regularly. Because of the inefficiency of previous DMARDs treatment for longer than 3 years, anti-TNF-α treatment with golimumab (GLM; Simponi®) was introduced. She did not have history of TB or contact with a patient with TB, and the interferon-γ release assay (IGRA) was negative before starting GLM treatment. Six months after starting GLM, the patient still had high RA activity (CRP level, 100.6 mg/L; pain visual analog scale (VAS) score, 80/100), and treatment was switched to adalimumab (ADA; Humira®). At first, the dose of ADA was 40 mg biweekly. After 1 month, the dose was increased to 80 mg biweekly, and then her RA activity gradually improved (CRP levels, 10.8 mg/L; VAS score, 35/100). Seven months after switching to ADA, the patient was taken to our hospital due to sudden high fever (up to 39.0°C) with dyspnea, falling to hypotensive shock. On the assumption of severe septic shock, she was admitted in the intensive care unit (ICU). Other physical examinations revealed cervical and axillary lymphadenopathies and digital ulcers. A chest X-ray and whole-body computed tomography (CT) scan showed no identifiable source of infection. Laboratory examination results are presented in Table 1. No findings suggestive of the existence of fungal infection were identified. Owing to positive peripheral blood smear for gram-positive coccus, she was treated with a course of antibiotics (meropenem 1 g thrice daily, linezolid 600 mg once daily). As a result of a positive blood culture for methicillin-sensitive Staphylococcus aureus, the antibiotic was changed to cefazolin (2 g thrice daily) three days later. The antibacterial treatment described above improved her general medical condition; however, intermittent low fever, high levels of CRP (Table 1), and lymph node swelling (Figure 1A) persisted for a week. Provisional diagnosis at this point was to rule out underlying TB or lymphoma. Upon re-examination, the result of IGRA (quantiFERON®-TB gold) was positive. As the result of excisional biopsy of the cervical lymph node, histological findings

| Items                  | Before GLM treatment | Before ADA treatment | At the onset of sepsis | When leaved ICU | When TB diagnosed | 3 weeks after TB treatment |
|------------------------|----------------------|----------------------|------------------------|----------------|-------------------|--------------------------|
| WBC (×10^9/L)          | 11.9                 | 11.5                 | 19.1                   | 4.7            | 7.0               | 5.3                      |
| RBC (×10^12/L)         | 4.07                 | 3.68                 | 4.66                   | 4.11           | 4.15              | 4.01                     |
| Hb (g/L)               | 103                  | 82                   | 120                    | 103            | 105               | 102                      |
| PLT (×10^9/L)          | 335                  | 531                  | 255                    | 168            | 256               | 206                      |
| AST (IU/L)             | 15                   | 8                    | 31                     | 22             | 25                | 19                       |
| ALT (IU/L)             | 9                    | 4                    | 10                     | 10             | 14                | 10                       |
| γ-GT (IU/L)            | 15                   | 14                   | 24                     | 30             | 24                | 25                       |
| LD (IU/L)              | 213                  | 201                  | 379                    | 268            | 282               | 242                      |
| CRE (μmol/L)           | 7.6                  | 70.0                 | 147.6                  | 39.8           | 35.4              | 46.0                     |
| UN (mmol/L)            | 7.7                  | 6.3                  | 16.2                   | 8.8            | 6.1               | 5.1                      |
| CK (IU/L)              | 20                   | 16                   | 636                    | 29             | 11                | 8                        |
| CRP (mg/L)             | 49.7                 | 100.6                | 182.8                  | 23.7           | 44.7              | 16.6                     |
| PCT (μg/L)             | -                    | -                    | 28.96                  | 0.59           | <0.1              | -                        |

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; LD, lactate dehydrogenase; UN, urea nitrogen; CK, creatine kinase; CRE, creatinine; CRP, C-reactive protein; PCT, procalcitonin.

Figure 1. (A) Computed tomographic demonstrated multiple enlargements of right cervical lymph nodes. (B) Histological findings of lymph node specimen show granulomatous inflammation with caseous necrosis, multinucleate giant cells, and epithelioid cells. (hematoxylin-eosin stain; original magnification, 200×)
showed granulomatous inflammation with caseous necrosis, multinucleate giant cells, and epithelioid cells (Figure 1B). In addition, positive acid-fast bacilli were seen using Ziehl-Neelsen stain, and the patient was histopathologically diagnosed with tuberculous lymphadenitis. After starting antitubercular agents (isoniazid 300 mg thrice daily, rifampicin 450 mg once daily, pyrazamide 1.2 g thrice daily, and ethambutol 750 mg thrice daily), she symptomatically improved and was later transferred to a hospital specializing in TB treatment.

3. Discussion

TNF-α has been implicated in the pathogenesis of many inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease. Biological drugs that inhibit TNF-α have markedly changed the treatment and outcome of these diseases (1). ADA is one of the TNF-α inhibitors, which is the first fully human, high-affinity, anti-TNF-α monoclonal antibody. With or without MTX or other DMARDs, ADA provided enough evidence of effectiveness in the treatment of adults with refractory RA (5). Although anti-TNF-α treatment is drastically effective in refractory patients with RA, an increased risk of infections often becomes a serious problem (2). Due to the immunological role of TNF-α, the infection caused by anti-TNF-α treatment of the greatest concern is TB; the risk of TB in patients with RA receiving anti-TNF-α treatment has been documented to range from 0.2 to 4% (6). Previous reports estimated extrapulmonary TB to constitute more than 50% of cases of TB in patients treated with anti-TNF-α drugs (4, 7, 8). In the patients treated with ADA, Dixon et al. previously reported that disseminated disease was the most common (40%), although lymph node disease was relatively low (10%) (7). In a recent study, IGRA was found to be more specific and sensitive than the tuberculosis skin test in patients with RA (9). In our case, however, despite the negative baseline screening with IGRA, the patient had converted IGRA 13 months after starting anti-TNF-α therapy. Although the clinical significance of IGRA conversions remains unclear, IGRA conversion was reportedly found in baseline IGRA-negative patients who developed TB late in the anti-TNF-α treatment (10). It is well known that TNF-α inhibitors increase the risk of TB, but extrapulmonary TB often induced by them is difficult to diagnose using a routine chest radiography or CT scanning. Hence, rescreening with IGRA is useful in suspected cases of TB, and excisional biopsy should be willingly performed to rule out extrapulmonary TB. In the case we presented, she had other risk factors, that is, advanced age at the start of anti-TNF-α treatment or concomitant use of corticosteroid, might contribute to the development of complex infections (2). We should keep in mind that careful follow-up and appropriate examinations are necessary in caring for patients administering immunosuppressive treatments including anti-TNF-α drugs.

References

1. Geiler J, Buch M, Mcdermott MF. Anti-TNF treatment in rheumatoid arthritis. Curr Pharm Des. 2011; 17:3141-3154.
2. Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A. Serious infections during anti-TNFα treatment in rheumatoid arthritis patients. Autoimmun Rev. 2009; 8:266-273.
3. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, Vinh DC. Anti-tumour necrosis factor agents and tuberculosis risk: Mechanisms of action and clinical management. Lancet Infect Dis. 2003; 3:148-155.
4. Keane J, Gershon S, Wise RP, Miralble-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med. 2001; 345:1098-1104.
5. Mease PJ. Adalimumab in the treatment of arthritis. Ther Clin Risk Manag. 2007; 3:133-148.
6. Cuomo G, D’abrsca V, Iacono D, Pantano I. The conversion rate of tuberculosis screening tests during biological therapies in patients with rheumatoid arthritis. Clin Rheumatol. 2017; 36:457-461.
7. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, B S R B R Control Centre Consortium, Symmons DP, BSR Biologics Register. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010; 69:522-528.
8. Alawmeh KM, Ayesh MH, Khassawneh BY, Saadeh SS, Smadi M, Bashaireh K. Anti-TNF therapy in Jordan: A focus on severe infections and tuberculosis. Biologics. 2014; 8:193-198.
9. Vassilopoulos D, Tsisikra S, Hatzara C, Podia V, Kandili A, Stamoulis N, Hadziyiannis E. Comparison of two γ-interferon release assays and tuberculin skin testing for tuberculosis screening in a cohort of patients with rheumatic diseases starting anti-tumor necrosis factor therapy. Clin Vaccine Immunol. 2011; 18:2102-2108.
10. Chen DY, Shen GH, Chen YM, Chen HH, Hsieh CW, Lan JL. Biphasic emergence of active tuberculosis in rheumatoid arthritis patients receiving TNFα inhibitors: The utility of IFNγ assay. Ann Rheum Dis. 2012; 71:231-237.

(Received May 2, 2018; Revised May 15, 2018; Accepted May 16, 2018)