Use of steroids to treat anti-tumor necrosis factor α induced tuberculosis-associated immune reconstitution inflammatory syndrome

Case report and literature review

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Abstract

Introduction: Individuals with tuberculosis (TB) who are being treated with anti-tumor necrosis factor α (anti-TNFα) for coexisting conditions may experience unexpected exacerbations of TB after the initiation of antituberculous therapy, so-called anti-TNFα-induced TB-immune reconstitution inflammatory syndrome (anti-TNFα-induced TB-IRIS). Anti-TNFα-induced TB-IRIS is often treated empirically with corticosteroids; however, the evidence of the effectiveness of corticosteroids is lacking and the management can be a challenge.

Patient concerns: A 32-year-old man on long-term infliximab therapy for Crohn disease visited a clinic complaining of persistent fever and cough that had started 1 week previously. His most recent infliximab injection had been administered 14 days before the visit. A chest X-ray revealed a left pleural effusion, and he was admitted to a local hospital.

Diagnosis: A chest computed tomography (CT) scan revealed miliary pulmonary nodules; acid-fast bacilli were found in a sputum smear and a urine sediment sample; and polymerase chain reaction confirmed the presence of Mycobacterium tuberculosis in both his sputum and the pleural effusion. He was diagnosed with miliary TB.

Interventions: Antituberculous therapy was started and he was transferred to our hospital for further management. His symptoms initially improved after the initiation of antituberculous therapy, but 2 weeks later, his symptoms recurred and shadows on chest X-ray worsened. A repeat chest CT scan revealed enlarged miliary pulmonary nodules, extensive ground-glass opacities, and an increased volume of his pleural effusion. This paradoxical exacerbation was diagnosed as TB-IRIS associated with infliximab. A moderate-dose of systemic corticosteroid was initiated [prednisolone 25 mg/day (0.5 mg/kg/day)].

Outcomes: After starting corticosteroid treatment, his radiological findings improved immediately, and his fever and cough disappeared within a few days. After discharge, prednisolone was tapered off over the course of 10 weeks, and he completed a 9-month course of antituberculous therapy uneventfully. He had not restarted infliximab at his most recent follow-up 14 months later.

Conclusion: We successfully managed a patient with anti-TNFα-induced TB-IRIS using moderate-dose corticosteroids. Due to the limited evidence currently available, physicians should consider the necessity, dosage, and duration of corticosteroids for each case of anti-TNFα-induced TB-IRIS on an individual patient-by-patient basis.

Abbreviations: anti-TNFα = anti-tumor necrosis factor-α, anti-TNFα-induced TB-IRIS = anti-tumor necrosis factor-α-induced tuberculosis-immune reconstitution inflammatory syndrome, CT = computed tomography, HIV = human immunodeficiency virus, TB = tuberculosis.

Keywords: corticosteroid, immune reconstitution inflammatory syndrome, infliximab, TNFα antagonist, tuberculosis

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1. Introduction

Anti-tumor necrosis factor α-induced tuberculosis immune reconstitution inflammatory syndrome (anti-TNFα-induced TB-IRIS) was first described in 2005. IRIS is a well-known phenomenon in the treatment of human immunodeficiency virus (HIV). HIV-associated IRIS is defined as the worsening of inflammatory symptoms during the immune reconstitution induced after starting antiretroviral therapy. Increased antigen levels, due to the death of *Mycobacterium tuberculosis* in response to antituberculous therapy, can trigger TB-IRIS in patients with HIV.

Although the incidence of anti-TNFα-induced TB-IRIS (4/56, 7%)[3] appears to be lower than that of HIV-associated TB-IRIS (median: 18%, range: 4–54%),[4] anti-TNFα-induced TB-IRIS may be triggered by a mechanism similar to that of HIV-associated TB-IRIS. The pathogenic mechanism of anti-TNFα-induced TB-IRIS is unknown. However, it may occur as a result of reconstituted immune responses against *M. tuberculosis* causing an uncontrolled inflammatory reaction.[5]

Appropriate management of anti-TNFα-induced TB-IRIS is a challenge.[6] Previous case reports have shown that anti-TNFα-induced TB-IRIS may respond to high-dose corticosteroids.[1] However, there is currently a lack of consensus regarding the use and dosage of corticosteroids for the treatment of anti-TNFα-induced TB-IRIS. Here, we report a case of anti-TNFα-induced TB-IRIS that was controlled using a moderate dose of systemic corticosteroids. In addition, we review published case reports of anti-TNFα-induced TB-IRIS and discuss its treatment, focusing on the use of corticosteroids. This study was reviewed and approved by the Clinical Research Ethics Committee of University of the Ryukyus.

2. Case report

A 32-year-old man who had been diagnosed with Crohn disease 7 years previously was admitted to our hospital with TB. Since diagnosis, his Crohn disease had been managed with infliximab. Before starting infliximab, he had tested negative for *M. tuberculosis* using an interferon-γ release assay. He visited a clinic complaining of persistent fever and cough that had started one week previously. His most recent infliximab injection had been administered 14 days before the visit. A chest X-ray revealed a left pleural effusion, and he was admitted to a local hospital. A computed tomography (CT) scan of his chest revealed miliary pulmonary nodules; acid-fast bacilli were found in a sputum smear and a urine sediment sample; and polymerase chain reaction confirmed the presence of *M. tuberculosis* in both his sputum and the pleural effusion. He was diagnosed with miliary TB and was started on antituberculous therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol). Six days after starting antituberculous therapy, he was transferred to the University of the Ryukyus Hospital in Okinawa, Japan, for further management.

The patient’s clinical course and chest X-ray findings are shown in Figure 1. His symptoms initially improved after starting antituberculous therapy, but his high fever recurred within 2 weeks of starting treatment, and his cough recurred within 3 weeks. Initially, his fever was thought to be a reaction to the antituberculous drugs, so his TB treatment regimen was changed to a combination of streptomycin, ethionamide, and levofloxacin on Day 15. However, his clinical condition continued to deteriorate. A repeat chest CT scan, done on Day 23, revealed enlarged miliary pulmonary nodules, extensive ground-glass opacities, and an increased volume of his pleural effusion (Fig. 2). This paradoxical exacerbation was diagnosed as

Figure 1. Clinical course and chest X-ray images of the patient. The patient experienced clinical deterioration about two weeks after starting antituberculous therapy. All clinical manifestations of TB-IRIS rapidly resolved after starting systemic corticosteroids.
The details of all 22 cases, including the one presented here, are summarized in Table 1. In all cases, TNF antagonists were initially withdrawn after anti-TNFα-induced TB-IRIS was diagnosed.

Generally, treatment of tuberculous meningitis requires corticosteroids in addition to antituberculous therapy. Corticosteroids are also frequently used to treat acute respiratory failure in individuals with TB. In our review, 6 of the 12 patients (50%) receiving corticosteroids had meningitis or respiratory failure at the time of IRIS onset and were therefore considered to have severe TB-IRIS. A systemic steroid is recommended as supplemental treatment for HIV-associated TB-IRIS, so using corticosteroids should be considered in severe cases of anti-TNFα-induced TB-IRIS.

Conversely, corticosteroids can have an adverse effect on infectious diseases by inhibiting immune responses against pathogens in a dose-dependent manner. A meta-analysis showed that using corticosteroids in combination with antituberculous drugs did not always result in a better clinical outcome compared with using antituberculous drugs alone. Therefore, some physicians may avoid the use of corticosteroids for the treatment of TB-IRIS, or provide as low a dose as possible. In our review, high-dose corticosteroids (≥40 mg/day or ≥1 mg/kg/day) were not always necessary. Two cases, including the case presented in this report, were treated with moderate-dose corticosteroids (7.5–39 mg/day), and corticosteroids were not used in 8 (36%) of the cases that we reviewed. Therefore, our review suggests that cases of anti-TNFα-induced TB-IRIS are not always severe, and corticosteroids may not be required. Given these findings, further discussions are needed to determine indications for corticosteroid use, and the optimal dose for treating anti-TNFα-induced TB-IRIS.

Three cases of severe anti-TNFα-induced TB-IRIS included in this review restarted treatment with TNF antagonists, and their anti-TNFα-induced TB-IRIS subsequently resolved. However, clinical data regarding restarting TNFα antagonists in patients with anti-TNFα-induced TB-IRIS is limited. TNFα antagonists have also been used to treat patients with steroid-refractory central nervous system TB, and can reduce the excessive inflammatory response to M. tuberculosis antigens and prevent IRIS. Although resuming treatment with TNFα antagonists in patients with anti-TNFα-induced TB-IRIS may be therapeutic, resuming treatment with TNF antagonists must be carefully considered because of TNFα’s critical role in controlling TB. If TNFα antagonists can be used to shorten the use of high-dose steroid therapy, they may provide a good alternative treatment for anti-TNFα-induced TB-IRIS. Rivoisy et al recommended that treatment with TNFα antagonists be resumed in severe cases of anti-TNFα-induced TB-IRIS, and Tanaka et al suggested that continuing TNFα antagonists may be effective for preventing anti-TNFα-induced TB-IRIS.

Among the cases that we reviewed, interval between the last administration of infliximab and the onset of IRIS in infliximab-associated cases (median: 6 weeks, range: 4–20 weeks) was longer than that of cases treated with other TNFα antagonists (median: 15 weeks, range: 5–30 weeks); however, this difference was not statistically significant (P = .22). This difference in the time of onset has been noted previously, and may be due to differences in the immune-recovery kinetics after anti-TNFα therapy has been discontinued.

In conclusion, we successfully managed a patient with anti-TNFα-induced TB-IRIS using moderate-dose corticosteroids.
**Table 1**

Summary of case reports of anti-tumor necrosis factor α-induced tuberculosis-associated immune reconstitution inflammatory syndrome.

| Case no. | Ref.            | Age | Underlying disease | TNFα antagonists/other immune-suppressant | TB site(s)       | Clinical features of TB-IRIS | Interval between recent anti-TNFα treatment and TB-IRIS onset (wk) | Interval between starting TB treatment and TB-IRIS onset (wk) | Corticosteroid regimen at onset† | Treatment for TB-IRIS | Outcome |
|----------|-----------------|-----|--------------------|------------------------------------------|------------------|-----------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|------------------------------|----------------------|----------|
| 1        | Belknap et al   | 73  | RA                 | IFX/PSL + MTX                            | Miliary, pleura  | Lung                         | 20 wk                                                            | 12 wk                                                            | None                         | Alive                |
| 2        | García Vidal et al | 49  | RA                 | IFX                                      | Miliary, lymph nodes | Lymph nodes                  | Not reported                                                    | 5 wk                                                            | None                         | Alive                |
| 3        | García Vidal et al | 48  | RA                 | IFX                                      | Miliary, lymph nodes | Lymph nodes                  | Not reported                                                    | 8 wk                                                            | None                         | Alive                |
| 4        | Yoon et al      | 38  | CD                 | IFX                                      | Skin             | Lymph nodes                  | Not reported                                                    | 15 wk                                                           | None                         | Alive                |
| 5        | Riosley et al   | 68  | CD                 | IFX                                      | Miliary, spleen  | Lymph nodes                  | Not reported                                                    | 12 wk                                                           | None                         | Alive                |
| 6        | Moureau et al   | 32  | PS                 | ADA                                      | Miliary, lymph nodes | Lymph nodes                  | Not reported                                                    | 8 wk                                                            | None                         | Alive                |
| 7        | Garcia Vidal et al | 48  | CD                 | IFX                                      | Miliary, lymph nodes | Lymph nodes                  | Not reported                                                    | 4 wk                                                            | None                         | Alive                |
| 8        | Unlu et al      | 45  | CD                 | IFX                                      | Lymph nodes      | Fever, malaise               | Not reported                                                    | 16 wk                                                           | None                         | Alive                |
| 9        | Arend et al     | 21  | CD                 | IFX                                      | Lymph nodes      | Fever, general discomfort    | Not reported                                                    | 4 wk                                                            | None                         | Alive                |
| 10       | Watanabe et al  | 75  | SAPHO syndrome     | ADA                                      | Lung             | Fever, fatigue, night sweats, cough, weight loss | 8 wk                                                            | <1 wk                                                           | PSL 10 mg                   | Alive                |
| 11       | Hess et al      | 17  | SAPHO syndrome     | ADA                                      | Meninges         | Headache, cerebral nerve palsy | 5 wk                                                            | 3 wk                                                            | None                         | Died                 |
| 12       | Falkenstern-Ge et al | 17  | SAPHO syndrome     | ADA                                      | Meninges         | Sature                       | 10 wk                                                           | 6 wk                                                            | None                         | Alive                |
| 13       | Current case    | 32  | CD                 | IFX                                      | Lung             | Fever, cough                 | 5 wk                                                            | 2 wk                                                            | PSL 25 mg (started with TB therapy) | Alive                |
| 14       | Tanaka et al    | 64  | RA                 | ADA                                      | Meninges         | Headache, nausea             | Not reported                                                    | 3 wk                                                            | None                         | Alive                |
| 15       | Sarsarum et al  | 70  | RA                 | IFX                                      | Pleura, peritoneum | Pleura                        | Not reported                                                    | 4 d                                                             | None                         | Alive                |
| 16       | Tran coo Marho et al | 44  | AS                 | IFX                                      | Lung, bone marrow | Lung                          | Fever                                                          | 8 wk                                                            | PSL 1 mg/kg                 | Alive                |
| 17       | Garcia Vidal et al | 56  | AS                 | IFX                                      | Lung, pleura, urinary system | Lymph nodes                  | Not reported                                                    | 8 wk                                                            | None                         | Alive                |
| 18       | Melboucy-Belkhir et al | 56  | AS                 | IFX                                      | Lung, pleura, lymph nodes, spleen, brain | Lymph nodes                  | Toxic syndrome                                                  | 20 wk                                                           | None                         | Alive                |
| 19       | Falkenstern-Ge et al | 37  | PS arthritis       | ADA                                      | Lung             | Fever                         | Not reported                                                    | 12 wk                                                           | None                         | Alive                |
| 20       | Walls et al     | 29  | RA                 | ADA/MTX                                 | Lung             | Fever, respiratory failure (initiated) | 4 wk                                                            | 2 wk                                                            | None                         | Alive                |
| 21       | Jorge et al     | 30  | RA                 | IFX                                      | Miliary, meninges | Meninges                      | 30 wk                                                           | None                         | None                         | Alive                |
| 22       | Kawamoto et al  | 75  | RA                 | ABT/IFX                                 | Lung             | Respiratory failure           | Not reported                                                    | 3 wk                                                            | None                         | Alive                |

**Note:**
- ABT = abatacept, ADA = adalimumab, AS = ankylosing spondylitis, AZA = azathioprine, CD = Crohn’s disease, DC = disseminated intravascular coagulation, IFX = infliximab, JIA = juvenile idiopathic arthritis, mPSL = methylprednisolone, MTX = methotrexate, PS = psoriasis, PSL = prednisolone, RA = rheumatoid arthritis, SAPHO = synovitis, acne, pustulosis, hyperostosis, and osteitis, TB = tuberculosis, TB-IRIS = tuberculosis-immune reconstitution inflammatory syndrome, TNFα = tumor necrosis factor-α.

**Abbreviations:**
- TNFα = tumor necrosis factor-α.
- TB-IRIS = tuberculosis-immune reconstitution inflammatory syndrome.

**Footnotes:**
- *Approximate interval.
- † PSL conversion: high dose: >40 mg/day (or >1 mg/kg/day); moderate dose: 7.5–30 mg/day.
The review of other case reports suggests that high-dose corticosteroids and/or TNFα antagonists may be needed for treating severe cases of anti-TNFα-induced TB-IRIS, but that some mild cases may not require treatment. Low-to-moderate doses of corticosteroids appear to be effective in treating most mild cases. However, as corticosteroids were not used for half of the cases that we reviewed, the use of corticosteroids should be carefully considered in patients with anti-TNFα-induced TB-IRIS that do not experience spontaneous remission. Due to the limited evidence currently available, physicians should consider the necessity, dosage, and duration of corticosteroids for each case of anti-TNFα-induced TB-IRIS on an individual patient-by-patient basis.

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Author contributions
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Daijiro Nabeya, Takeshi Kinjo, and Kazutaka Yamanai. The first draft of the manuscript was written by Daijiro Nabeya. All authors provided comments on subsequent drafts of the manuscript, and read and approved the final draft.

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