Central Nervous System Manifestations of Tuberculosis-associated Immune Reconstitution Inflammatory Syndrome during Adalimumab Therapy: A Case Report and Review of the Literature

Toru Tanaka, Akimasa Sekine, Yoshiya Tsunoda, Hiroyuki Takoi, Shin-Yuan Lin, Yohei Yatagai, Kenji Hayasihara and Takefumi Saito

Abstract

A 64-year-old neurologically asymptomatic woman with rheumatoid arthritis who was treated with the tumor necrosis factor (TNF)-α antagonist adalimumab developed disseminated tuberculosis (TB). After receiving anti-TB therapy and discontinuing adalimumab, she exhibited paradoxical worsening due to immune reconstitution inflammatory syndrome (IRIS) with the appearance of meningitis and brain tuberculomas. This case indicates that continuing anti-TNF therapy may be necessary to prevent IRIS in patients who develop TB, particularly disseminated TB, during the course of anti-TNF therapy. In addition, careful screening for central nervous system (CNS) TB should be performed prior to the initiation of therapy, as even neurologically asymptomatic patients can develop CNS manifestations of IRIS.

Key words: adalimumab, anti-TNF therapy, tuberculosis, central nervous system tuberculosis, immune reconstitution inflammatory syndrome

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Introduction

Anti-tumor necrosis factor (TNF) therapy increases the risk of tuberculosis (TB) (1). Discontinuing anti-TNF therapy during treatment for TB sometimes results in the reconstitution of the immune system and may contribute to “paradoxical worsening.” This phenomenon, known as immune reconstitution inflammatory syndrome (IRIS), is well recognized in human immunodeficiency virus (HIV) patients treated with anti-TB and anti-HIV therapy (2).

We herein report a case of disseminated TB during anti-TNF therapy in which central nervous system (CNS) manifestations of IRIS developed after the discontinuation of anti-TNF therapy and initiation of anti-TB therapy.

Case Report

A 64-year-old woman was referred to our hospital on suspicion of miliary TB. She had been diagnosed with rheumatoid arthritis in 1988 and began treatment with adalimumab therapy in March 2010. Screening for TB prior to the initiation of adalimumab therapy revealed normal chest X-ray findings and a positive tuberculin skin test. However, a chest computed tomography (CT) scan and interferon-γ-release assay for tuberculosis were not performed. She subsequently received no prophylactic anti-TB therapy despite the positive tuberculin skin test.

At the end of July 2010, the patient complained of fever and cervical swelling. A chest X-ray and CT scan showed numerous miliary nodules in both lung fields (Fig. 1a, b) as well as left cervical, left supraclavicular and mediastinal lymphadenopathy (Fig. 1c) and multiple nodules in the...
spleen and kidneys. *Mycobacterium tuberculosis* was confirmed on polymerase chain reaction (PCR) and cultures of the sputum and urine, leading to a diagnosis of disseminated TB. The isolated *M. tuberculosis* strain was susceptible to all anti-TB drugs.

Immediately after diagnosis, an anti-TB regimen comprising isoniazid, rifampicin, pyrazinamide and ethambutol was initiated, and the dose of adalimumab was discontinued. After receiving this therapy, the patient’s symptoms progressively improved.

The patient exhibited no abnormal neurological findings prior to the administration of TB therapy; however, three weeks later, she presented with a headache and nausea. Brain magnetic resonance imaging (MRI) showed multiple enhanced lesions indicating brain tuberculomas (Fig. 2a). Moreover, a cerebrospinal fluid (CSF) analysis confirmed the presence of meningitis with a leukocyte concentration of 23/mm³ (neutrophils: 68%, lymphocytes: 32%), increased protein level of 62.0 mg/mL and decreased glucose level of 33 mg/dL. Acid-fast bacilli were negative, and *M. tuberculosis* was confirmed on polymerase chain reaction (PCR) and cultures of the sputum and urine, leading to a diagnosis of disseminated TB. The isolated *M. tuberculosis* strain was susceptible to all anti-TB drugs.

**Figure 1.** Chest imaging performed prior to anti-TB therapy. A chest X-ray showed numerous nodules in both lung fields (a). Chest CT showed miliary nodules in both lung fields and necrotic mediastinal lymphadenopathy (b, c).

**Figure 2.** Brain MRI performed at the time of paradoxical worsening showed multiple enhanced lesions indicative of brain tuberculomas (a). Chest CT showed worsening of the left cervical and supraclavicular lymph node swelling (b, c).
# Table. Reports of the Development of IRIS Following the Discontinuation of Anti-TNF Therapy in the Previous Literature and the Current Case

<table>
<thead>
<tr>
<th>TNF antagonist</th>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Underlying disease</th>
<th>Clinical manifestations of TB at diagnosis</th>
<th>Time to IRIS</th>
<th>Clinical manifestation of IRIS</th>
<th>Specific treatment for IRIS</th>
<th>outcome</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>1</td>
<td>F</td>
<td>17</td>
<td>SAPHO syndrome</td>
<td>Disseminated (miliary TB, pleural and pericardial effusion, brain tuberculosis, and meningitis)</td>
<td>4 weeks</td>
<td>Worsening meningitis and brain tuberculosis</td>
<td>Corticosteroids, ventriculo-peritoneal shunt</td>
<td>alive</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M</td>
<td>32</td>
<td>Psoriasis</td>
<td>Disseminated (miliary TB and lymph node disease)</td>
<td>8 weeks</td>
<td>New-onset lymphadenopathies at several sites</td>
<td>None</td>
<td>alive</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F</td>
<td>29</td>
<td>RA</td>
<td>Pulmonary TB</td>
<td>13 days</td>
<td>Worsening lung infiltrate</td>
<td>Corticosteroids (PSL 2.0 mg/kg), readministration of adalimumab</td>
<td>alive</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>F</td>
<td>68</td>
<td>Inflammatory bowel disease</td>
<td>Disseminated (Multiple nodules in the liver and spleen)</td>
<td>4 weeks</td>
<td>New-onset lymphadenopathies at several sites and a cavity in the lung</td>
<td>None</td>
<td>alive</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>F</td>
<td>64</td>
<td>RA</td>
<td>Disseminated (Miliary TB, lymph node disease, and multiple nodules in the kidney and spleen)</td>
<td>3 weeks</td>
<td>New-onset meningitis and brain tuberculosis, and recurrent lymphadenopathies at several sites</td>
<td>Corticosteroids (PSL 30mg/day)</td>
<td>alive</td>
<td>Our patient</td>
</tr>
<tr>
<td>infliximab</td>
<td>6</td>
<td>F</td>
<td>56</td>
<td>Ankylosing spondylitis</td>
<td>Disseminated (miliary TB, lymph node disease, and brain and splenic nodules)</td>
<td>12 weeks</td>
<td>Recurrent lymphadenopathies at several sites</td>
<td>Corticosteroids (PSL 1.0mg/kg/day), tinagurin</td>
<td>alive</td>
<td>2</td>
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<tr>
<td></td>
<td>7</td>
<td>M</td>
<td>24</td>
<td>Crohn disease</td>
<td>Pulmonary TB</td>
<td>2 weeks</td>
<td>New-onset lymphadenopathies at several sites and miliary TB</td>
<td>None (continuation of PSL and AZA)</td>
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<td></td>
<td>8</td>
<td>M</td>
<td>44</td>
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<td>4 weeks</td>
<td>Not described</td>
<td>Corticosteroids (PSL 1.0 mg/kg/day)</td>
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<tr>
<td></td>
<td>9</td>
<td>M</td>
<td>20</td>
<td>Juvenile idiopathic arthritis</td>
<td>Disseminated (miliary TB)</td>
<td>24 weeks</td>
<td>New-onset meningitis and brain tuberculosis</td>
<td>Corticosteroids (PSL 75 mg/day), MTX, readministration of infliximab</td>
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<tr>
<td></td>
<td>10</td>
<td>F</td>
<td>49</td>
<td>RA</td>
<td>Disseminated (miliary TB and lymph node disease)</td>
<td>5 weeks</td>
<td>Worsening supravacular lymphadenopathy</td>
<td>Surgical excision of the lymph node disease</td>
<td>alive</td>
<td>13</td>
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<tr>
<td></td>
<td>11</td>
<td>F</td>
<td>48</td>
<td>RA</td>
<td>Disseminated (miliary TB and lymph node disease)</td>
<td>8 weeks</td>
<td>New-onset lymphadenopathies at several sites</td>
<td>Surgical excision of the lymph node disease</td>
<td>alive</td>
<td>13</td>
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<tr>
<td></td>
<td>12</td>
<td>M</td>
<td>56</td>
<td>Ankylosing spondylitis</td>
<td>Pulmonary and pleural TB</td>
<td>8 weeks</td>
<td>Worsening infiltrates and pleural effusion</td>
<td>Corticosteroids (PSL 1.0mg/kg/day)</td>
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<td>13</td>
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<tr>
<td></td>
<td>13</td>
<td>M</td>
<td>21</td>
<td>Crohn disease</td>
<td>Anal TB</td>
<td>16 weeks</td>
<td>New-onset inguinal lymphadenopathy</td>
<td>NSAIDs</td>
<td>alive</td>
<td>13</td>
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<tr>
<td></td>
<td>14</td>
<td>M</td>
<td>38</td>
<td>Crohn disease</td>
<td>Disseminated (miliary TB and multiple nodules in the spleen)</td>
<td>12 weeks</td>
<td>New-onset lymphadenopathies at several sites</td>
<td>Surgical excision of lymph node disease</td>
<td>alive</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>F</td>
<td>73</td>
<td>RA</td>
<td>Pulmonary and pleural TB</td>
<td>12 weeks</td>
<td>Worsening lung infiltrates</td>
<td>None</td>
<td>alive</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>M</td>
<td>70</td>
<td>RA</td>
<td>Disseminated (Pleurale effusion and ascites)</td>
<td>4 days</td>
<td>Reaccumulation of pleural effusion</td>
<td>Corticosteroids (PSL 60mg/day)</td>
<td>alive</td>
<td>16</td>
</tr>
</tbody>
</table>

sis was not detected on PCR or a culture of the CSF. At the time of the CNS TB diagnosis, the chest X-ray and cervical lymph node findings were not exacerbated.

Prednisolone (PSL; 30 mg/day) was used to treat the TB meningeal. Because the patient’s CNS symptoms gradually improved and the cervical lymph nodes decreased in size, the dose of PSL was initially tapered and eventually discontinued after four weeks. However, two weeks after discontinuing PSL, she presented with worsening of the left cervical and supraventricular lymph node swelling (Fig. 2b, c), which resolved following the readministration of PSL. Finally, the patient successfully completed a 12-month course of the anti-TB therapy regimen, and the lung nodules and lymphadenopathies disappeared.

**Discussion**

We herein described the case of a patient who developed disseminated TB during the course of anti-TNF therapy with adalimumab. After discontinuing adalimumab and initiating TB therapy, the patient developed CNS manifestations of IRIS, although neurological symptoms were initially absent.

The clinical course of this patient highlights two important issues. First, it may be necessary to continue anti-TNF therapy in order to prevent IRIS in patients who develop TB, particularly disseminated TB, during treatment with anti-TNF therapy. Second, careful screening for CNS TB using brain MRI and CSF analyses should be performed before initiating TB therapy because even neurologically asymptomatic patients may develop CNS TB involvement of IRIS during their clinical course.

It may be necessary to continue anti-TNF therapy in order to prevent IRIS in patients who develop TB, particularly disseminated TB, during the course of anti-TNF therapy. Our patient developed new-onset CNS TB and aggravated multiple lymphadenopathies manifesting as IRIS after discontinuing adalimumab and receiving anti-TB therapy, and corticosteroid therapy was subsequently required to treat the IRIS. It has been postulated that IRIS develops as a result of an excessive inflammatory response. In patients who develop TB during the course of anti-TNF treatment, discontinuing anti-TNF therapy may help to restore the immune response and thus contribute to the onset of IRIS (3). To the best of our knowledge, there are 16 reported cases, including this case, in which the patients developed TB during treatment with anti-TNF therapy and experienced IRIS after discontinuing anti-TNF therapy and receiving anti-TB therapy, as shown in Table. Interestingly, 10 of the 16 (63%) patients with IRIS had disseminated TB, indicating that IRIS is more likely to occur in cases of disseminated TB, as previously reported in HIV-infected patients with IRIS (4, 5). At the time of TB diagnosis, adalimumab and infliximab were used in five and 11 patients, respectively. The time from discontinuation of anti-TNF therapy to the onset of IRIS tended to be longer under infliximab therapy (median: 56 days; range 4 days to 6 months) than under adalimumab therapy (median: 28 days; 13 to 56 days), although the difference was not statistically significant (p=0.11, Mann-Whitney U test). This difference may be due to the shorter half-life of adalimumab compared with that of infliximab (6). Regarding the management of IRIS, eight of the above patients (50%) required new treatment with or an increased dose of corticosteroids. It is known that corticosteroid therapy may reduce the rate of TB-induced TNF production and inhibit IRIS development (7). However, two of the patients were resistant to high-dose corticosteroids and required the readministration of anti-TNF therapy for life-threatening IRIS with CNS and lung lesions, respectively (Cases 3 and 9 in Table). This indicates that anti-TNF therapy inhibits an excessive inflammatory response and thus prevents IRIS more effectively and safely than corticosteroid therapy at the time of TB therapy.

The onset of latent CNS TB should be considered in patients with disseminated TB receiving anti-TNF therapy. Our patient developed CNS TB during TB therapy, although neurological symptoms were initially absent. In addition, all previously reported patients with CNS manifestations of IRIS had disseminated TB at the time of TB diagnosis (Cases 1 and 9 in Table). Considering our present case in addition to these two cases, the development of disseminated TB appears to be a risk factor for CNS manifestations of IRIS. In this context, based on a literature review of patients with HIV-related TB, 23 of 190 patients (12%) who developed IRIS after receiving anti-TB and anti-HIV therapy displayed CNS manifestations of IRIS, 13-30% of whom died (8). Importantly, the majority of patients who presented with CNS manifestations of IRIS had no neurological symptoms prior to the initiation of anti-HIV therapy; this finding is attributable to subclinical seeding of TB into neurologic tissues, thus provoking an inflammatory response at the time of IRIS (5). As in HIV-positive patients, the onset of CNS manifestations of IRIS due to the discontinuation of anti-TNF therapy may also be associated with high mortality. Hence, brain MRI and CSF analyses should be performed to screen for latent CNS TB before administering therapy, even in neurologically asymptomatic patients.

In conclusion, continuing anti-TNF therapy may be effective for preventing IRIS in patients who develop TB, particularly disseminated TB, during treatment with anti-TNF therapy. In addition, careful screening for CNS TB should be performed prior to the initiation of therapy, taking into consideration the potential for fatal CNS manifestations of IRIS, even in neurologically asymptomatic patients.

The authors state that they have no Conflict of Interest (COI).

**References**


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