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<tr>
<th>Citation</th>
<th>Clinical Journal of Gastroenterology. 15(3): 592–597</th>
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<tbody>
<tr>
<td>Issue Date</td>
<td>2022-06</td>
</tr>
<tr>
<td>Published</td>
<td>2022-03-04</td>
</tr>
<tr>
<td>Type</td>
<td>Journal Article</td>
</tr>
<tr>
<td>Textversion</td>
<td>Author</td>
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<td>Rights</td>
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</tr>
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<td>DOI</td>
<td><a href="https://doi.org/10.1007/s12328-022-01616-6">https://doi.org/10.1007/s12328-022-01616-6</a></td>
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A case of paradoxical response during anti-tuberculosis treatment in a patient with ulcerative colitis

Shuhei Hosomi*, Naoko Sugita, Atsushi Kanamori, Masaki Ominami, Koji Otani, Noriko Kamata, Fumio Tanaka, Yasuaki Nagami, Koichi Taira, Yasuhiro Fujiwara

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Keywords

Tuberculous pleuritis, paradoxical response, ulcerative colitis, anti-tumor necrosis factor-α antibody

Abstract

Emerging anti-tumor necrosis factor (TNF)-α antibodies therapy changed treatment strategy to inflammatory bowel diseases because of the efficacy. However, TNF-α inhibitor can be associated
with an increased risk of infectious complications, especially tuberculosis. A 71-year-old female
with steroid-dependent ulcerative colitis (UC) was admitted due to relapse of UC with
endoscopically severe active. Golimumab and adjunctive prednisolone started with 30 mg daily
resulted in clinical remission. However, she had general fatigue and fever at the time of seventh
injection of golimumab without abdominal symptoms. Based on positive interferon-gamma release
assay, polymerase chain reaction positive for tuberculosis (TB) in pleural fluid, and chest computed
tomography, she was diagnosed as tuberculous pleuritis. Standard anti-TB treatment (isoniazid,
rifampicin, ethambutol, and pyrazinamide) was started without cessation of golimumab, because
cessation of TNF-α inhibitors during anti-TB treatment could cause the paradoxical response by
skewing from regulatory to inflammatory immune responses. However, four weeks after initiation of
anti-TB treatment, she got fever-up and pleural effusion increased. We then started prednisolone 30
mg daily as diagnosis of paradoxical response, resulting in improving the symptoms. This is a
suggestive case of paradoxical response during anti-TB treatment despite continuous TNF-α
inhibitors.
Introduction

Biologics including anti-tumor necrosis factor (TNF)-α inhibitor, which can reduce hospitalizations, surgery, and recurrence, have been widely used for patients with ulcerative colitis (UC) \(^1\). However, TNF-α inhibitor can be associated with an increased risk of infectious complications, especially tuberculosis (TB) \(^2\). TNF-α inhibitor should be generally discontinued for patients with active TB prior to anti-TB treatment \(^3\). However, discontinuation of TNF-α inhibitor could contribute to TB worsening after initial improvement by TB treatment, known as the paradoxical response \(^4\). \(^5\).

Limited evidence regarding the paradoxical response during anti-TB treatment for inflammatory bowel disease (IBD) patients treated with biologics is currently available. We herein report a case of tuberculous pleuritis in patient with UC, who developed paradoxical response during anti-TB treatment even though TNF-α inhibitor was continued.

Case Report

A 71-year-old female, who was diagnosed as pancolitis type UC at age 50, was maintaining clinical remission on monotherapy of mesalazine initially. Azathioprine 50 mg daily was started at age 65 due to steroid-dependent clinical course. The azathioprine had been discontinued after endoscopic remission was confirmed at age 67, as she had nausea and dizziness probably caused by azathioprine. The remission had been kept on monotherapy of mesalazine (3.6 g daily) since that time.
The patient relapsed with symptoms of diarrhea (five times per day) and fresh blood one month before admission, and the total colonoscopy revealed moderately active colitis up to transverse colon. Then, intensive granulocyte-monocyte apheresis (GMA) was initiated (twice a week). Her clinical symptoms were getting worse after 6 sessions of GMA, therefore, she was admitted with symptoms of watery diarrhea (10 times per day), obvious fresh blood, tenesmus, and abdominal pain. Blood test data revealed increase levels of serum C-reactive protein (CRP) (1.76 mg/dL) and erythrocyte sedimentation rate (ESR) (29 mm at 1hr). The total colonoscopy showed that continuous inflammation from rectum to ascending colon with geographic ulcers (Figure 1). The biopsy specimens revealed negative for cytomegalovirus based on hematoxylin and eosin staining and immunohistochemistry. The stool examination showed no evidence of specific bacterial infection including *Clostridium difficile*. Regarding TB infection, interferon (IFN)-gamma release assay (IGRA) (ELISPOT: enzyme-linked immunosorbent spot test) was negative and chest X-ray had no evidence of TB infection. She had no medical history of TB infection. Golimumab was started on day seven of the first admission under the diagnosis of recurrence of steroid-dependent UC. She had a partial clinical response to Golimumab initially and was discharged after second injection of Golimumab. However, her symptoms were gradually getting worse again after third infection of Golimumab, then, adjunctive prednisolone 30 mg daily was added one week after the Golimumab injection. Although the adding prednisolone resulted in clinical remission rapidly and Golimumab
was continued with tapering prednisolone, she had general fatigue and fever at the time of six
injection of Golimumab without abdominal symptoms (Figure 1).

The patient had increased levels of CRP and ESR on blood test and was admitted, however, she had
no symptoms and findings of urinary tract infection, exacerbation of colitis, drug-induced lupus
erythematosus, such as arthritis, dermatitis, based on laboratory data (Table 1). Chest X-ray and
computed tomography revealed left pleural effusion without any active lesions on lung field (Figure
1). Based on the positive IGRA (ELISPOT) result, increased level of adenosine deaminase in pleural
fluid, and polymerase chain reaction (PCR) positive for TB in pleural fluid (Table 1), she was
diagnosed as tuberculous pleuritis. Standard anti-TB treatment (isoniazid, rifampicin, ethambutol,
and pyrazinamide) was started without cessation of Golimumab. Four weeks after initiation of
anti-TB treatment, fever-up and general fatigue occurred again, and her pleural effusion was
increased (Figure 1). We then started prednisolone 30 mg daily for diagnosis of paradoxical response
under the administration, resulting in improving the symptoms. Golimumab was discontinued after
the paradoxical response occurred, but she has not had UC recurrence on monotherapy of mesalazine.
The follow-up colonoscopy at one year after the administration for paradoxical response showed
endoscopic remission.
Discussion

With the accumulation of a large body of evidence about long-term efficacy and safety of anti-TNF inhibitor in IBD, more anti-TNF inhibitor have been used for better outcome. As TNF-α is a key molecule of immune response for TB infection \(^6\), considering the risk of TB reactivation in patients treated with TNF-α inhibitor is important, especially in TB-endemic area. As shown in Figure 2, countries with the high incidence of TB are mainly those in the Asia-Pacific region, and the TB incidence (https://www.who.int/teams/global-tuberculosis-programme/data) and prevalence of IBD\(^7\) are negatively correlated. In these Asian countries, the prevalence of IBD is increasing in the last few decades, therefore, strategies for monitoring the new TB infection and reactivation of latent TB are needed.

Reactivation of latent TB is increased in patients with IBD receiving a TNF-α inhibitor treatment \(^8\), especially in TB-endemic areas, such as Asian countries \(^9\). Reactivation of latent TB infection rather than a new infection is considered to be the primary cause of active TB during TNF-α inhibitor therapy \(^10\), therefore, screening for latent or active TB should always be performed prior to commencing TNF-α inhibitors. IGRAs; in vitro blood tests of cell-mediated immune response, which measure IFN-gamma releasing from T cells following stimulation by antigens unique to *Mycobacterium tuberculosis* or a few other mycobacteria\(^11\), are known to be preferred over tuberculin skin test in Bacille Calmette-Guérin (BCG) -vaccinated individuals, because tuberculin skin test, but not IGRAs, exhibits cross-reactivity with the BCG vaccine \(^12\). Since IGRAs could be
falsely negative under conditions of immunosuppression and low peripheral lymphocyte counts, a combination examination of adequate interviews, chest X-ray, tuberculin skin test, and IGRA is required for the diagnosis of LTBI. The present patient developed IGRA-positive tuberculous pleuritis, even though the patient had no medical history of TB infection, and negative chest X-ray, for TB and negative IGRA before the introduction of Golimumab. In fact, several papers showed that negative screening results could not exclude the risk of TB reactivation during TNF-α inhibitor therapies 13, suggesting that all patients who initiate TNF-α inhibitors need to be closely monitored for reactivation of TB.

TNF-α have a protective function against the reactivation of TB, and also have another aspect of involvement in the development of paradoxical worsening during TB treatment, which is known to be paradoxical response/reaction 14. This phenomenon is also referred as TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) 15, which is commonly associated with antiretroviral therapy in patients with human immunodeficiency virus (HIV) 16. The mechanisms of TB-IRIS are assumed by activation of macrophages by abundant proinflammatory cytokines (e.g. interferon-γ and TNF-α) released from increased CD4+ T cells, resulting in inflammasome activation and tissue damage 14,17. Paradoxical response is generally defined by a clinical or radiological worsening of TB lesions or the development of new lesions, in patients receiving anti-TB treatment who initially improved on the treatment. The present case initially improved CRP after TB treatment,
however, four weeks after initiation of anti-TB treatment, her clinical symptoms and radiological findings got worse (Figure 1). Then we diagnosed the present case as paradoxical response in TB. The first coherent report of TNF-α inhibitors-associated TB paradoxical response is case series reported by García Vidal C, describing that 67% of patients (4 / 6) with TNF-α inhibitors-associated TB worsening developed paradoxical response after discontinuation of TNF-α inhibitors. Subsequent larger registry study revealed that the incidence of anti-TNFα inhibitors-associated TB paradoxical response (4/56, 7%) 5. This study also showed that not only corticosteroids but also restart of TNF-α inhibitor were effective for the paradoxical response, implying that the discontinuation of TNF-α inhibitors might be one of triggers of development of the paradoxical response.

From the viewpoint of prevention of the paradoxical response, whether TNF-α inhibitors should be discontinued or not is controversial. Matsumoto et al reported that three of 13 patients with discontinuation of TNF-α inhibitors developed the paradoxical response, whereas seven patients without discontinuation did not. Moreover, the study also revealed that the sputum culture positive period was not prolonged by TNF-α inhibitors treatment18, suggesting that TNF-α inhibitors should be continued during TB-treatment. Since the symptoms that were initially improved by TB treatment got worse four weeks after the initiation of anti-TB treatment, we diagnosed this case as paradoxical response; however, this exacerbation might simply develop under immunosuppressive status for TB, which can be caused by anti-TNFα antibody. To date, there have been not enough evidence to
determine whether the paradoxical response by discontinuation of TNF inhibitors or the exacerbation of TB due to continued TNF inhibitors use are more frequently seen during anti-TB treatment. We therefore believe that the present case could serve as a starting point for that discussion.

Discontinuation of TNF-α inhibitors is generally recommended when the TB reactivation develops as described in consensus statement of European Crohn's and Colitis Organisation (ECCO) and Asian Organization for Crohn’s and Colitis and Asian Pacific Association of Gastroenterology (AOCC-APAGE) so far; however, further large cohort studies will be needed to clarify this issue.

This is a suggestive case of paradoxical response requiring corticosteroid during anti-TB treatment despite continuous TNF-α inhibitor.
Figure legends:

Figure 1. Clinical course of the present case

Figure 1

- **Tuberculous pleuritis**
- **Total colonoscopy**
- **Paradoxical response**

**CRP (mg/dL)**

- **GLM** 100mg
- **GMA**
- **PSL 30mg**
- **EB / PZA**
- **INH / RFP**

**Mesalazine 3.6g**

**Mesalazine 4.8g**

- Admission
- 1 2 3 4 5 6 7 8 9 10 11 12
- **partial Mayo score**
- **(Month)**
Figure 2. Relationship between tuberculosis incidence and prevalence of inflammatory bowel disease.

The data of tuberculosis (TB) incidence and inflammatory bowel disease (IBD) prevalence were collected from data by the WHO Global Tuberculosis Programme (https://www.who.int/teams/global-tuberculosis-programme/data) and publication by Ng SC et al7.

IBD: inflammatory bowel disease, TB: tuberculosis
Figure 2

The scatter plot illustrates the relationship between TB incidence (per 100,000 population) and IBD prevalence (per 100,000 population per year) across various countries and regions. The countries represented include:

- Algeria
- Australia
- Bosnia and Herzegovina
- Brazil
- Canada
- China
- Croatia
- Denmark
- Germany
- Hungary
- India
- Italy
- Japan
- Kuwait
- Lebanon
- Malaysia
- Netherlands
- New Zealand
- Portugal
- Puerto Rico
- South Korea
- Spain
- Sri Lanka
- Sweden
- Switzerland
- Turkey
- United Kingdom of Great Britain and Northern Ireland
- United States of America

The countries are color-coded based on regions:
- North America
- South America
- Oceania
- Eastern Asia
- South-Eastern & Southern Asia
- Western Asia
- Europe
- Africa

The plot shows a wide range of incidence and prevalence values, with some countries having high incidences and lower prevalences, and others having lower incidences with higher prevalences.
Acknowledgments: This study received no specific funding and grants.

Informed Consent: Informed consent was obtained from the patient for this case report.

Conflict of Interests: Conflict All authors disclose no conflicts of interests.

References


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<td>/mm$^3$</td>
<td>TP</td>
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<td>RBC</td>
<td>502</td>
<td>/10$^6$/μL</td>
<td>Alb</td>
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<tr>
<td>Hb</td>
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<tr>
<td>Ht</td>
<td>41.1</td>
<td>%</td>
<td>Cre</td>
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<tr>
<td>MCV</td>
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<td>mm$^3$</td>
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<td>CRP</td>
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<td>mg/dL</td>
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<td>Neutrophil</td>
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<td>Glucose</td>
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<tr>
<td>Mycobacterium intracellulare</td>
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Table 1. Laboratory data on the second admission