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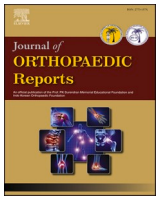

Case Report

# Reactivation of latent tuberculosis infection following initiation of tofacitinib therapy for rheumatoid arthritis: A case report

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ABSTRACT

*Background:* Latent tuberculosis infection (LTBI) reactivation is a well-known risk associated with immunosuppressive therapies employed in the treatment of rheumatoid arthritis (RA). Tofacitinib, an approved medication for RA that inhibits Janus kinases, has been associated with an elevated risk of TB reactivation. However, diagnosing TB in RA patients can be challenging due to the atypical presentation of the disease in this population.
*Case report:* In this report, we present the case of a 54-year-old male with a history of RA who presented with symptoms of productive cough, fever, and night sweats. The patient had been receiving sulfasalazine, methotrexate, folic acid, and prednisolone for RA, but due to disease progression, tofacitinib was initiated six weeks prior. Upon examination, the patient displayed respiratory distress and bilateral lung crepitations. Initial treatment with broad-spectrum antibiotics for suspected community-acquired pneumonia proved ineffective, and a chest X-ray revealed bilateral infiltrates in the upper lobes. The patient disclosed a history of previously treated TB infection twelve years ago. Subsequent investigations confirmed reactivation of LTBI, supported by positive results from the Mantoux test and interferon-gamma release assay (IGRA). Tofacitinib and methotrexate were discontinued, and the patient was initiated on the standard four-drug anti-TB therapy. However, the patient's RA symptoms worsened, necessitating the reintroduction of methotrexate at a reduced dosage and the addition of hydroxychloroquine to the treatment regimen. The patient tolerated the TB therapy well and experienced an improvement in RA symptoms with the combination therapy.
*Conclusion:* This case underscores the significance of considering the risk of LTBI reactivation in RA patients receiving tofacitinib therapy or any other immunosuppressive treatment. Healthcare providers should maintain a high level of suspicion for TB in RA patients with a history of latent TB infection, particularly in regions where TB is prevalent. Additionally, alternative treatment options should be considered to balance the management of RA and the risk of infectious complications. Rapid diagnosis and treatment of active TB are crucial to prevent complications. A multidisciplinary approach involving rheumatologists and pulmonologists is essential for the optimal management of these patients.

## 1. Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that impacts nearly 1% of people globally. The condition is marked by inflammation of the synovial tissue and destruction of joints, resulting in reduced quality of life, disability, and pain.[1] In the past few years, there has been a significant advancement in the management of RA due to the development of specific therapies like biological Disease-modifying antirheumatic drugs (DMARDs) and Janus kinase (JAK) inhibitors. These medications can suppress the immune system and pose a higher risk of infections in susceptible individuals. RA patients, especially in countries with a high prevalence of tuberculosis, are particularly vulnerable to TB infections.[2]

Tuberculosis (TB) remains a major global health concern, with a significant burden on public health systems worldwide. According to the World Health Organization (WHO), TB is one of the top 10 causes of death worldwide, surpassing HIV/AIDS in mortality rates.[3] In 2020, an estimated 10 million people developed TB, with 1.4 million deaths attributed to the disease.[3] The majority of TB cases occur in low- and middle-income countries, particularly in regions with limited healthcare

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resources and high population density. Factors such as poverty, malnutrition, inadequate access to healthcare, and the HIV epidemic contribute to the persistence of TB.[3,4]

Rheumatoid arthritis patients face an increased risk of developing TB due to their compromised immune system resulting from the disease itself or its treatment. The immune-suppressing effects of DMARDs, particularly biological DMARDs and JAK inhibitors, make RA patients more susceptible to TB infection.[5] Studies have shown that the risk of developing active TB in RA patients receiving these therapies is higher compared to the general population.[5,6] Moreover, TB infection in RA patients can present diagnostic challenges, as the clinical and radiological features of TB can overlap with those of RA.[6]

Tofacitinib, an FDA-approved JAK inhibitor used for treating rheumatoid arthritis (RA), reduces inflammation by inhibiting JAK enzymes involved in cytokine signalling pathways. This leads to decreased production of pro-inflammatory cytokines and immune cell activation. Clinical trials have shown its efficacy in improving RA symptoms and physical function. However, the use of tofacitinib is associated with an increased susceptibility to infections, including tuberculosis (TB). RA patients on immunosuppressive therapy already have a higher risk of latent TB infection (LTBI), which, if reactivated, can progress to active TB disease. Tofacitinib further elevates the risk of TB by suppressing the production of interferon-gamma, a crucial component of the body's defence against TB.[7,8]

This case report highlights a patient with rheumatoid arthritis (RA) who developed tuberculosis (TB) while on tofacitinib treatment. It underscores the challenges of managing TB in patients on immunosuppressive therapy, stressing the importance of careful screening, monitoring, and prompt treatment of TB in RA patients receiving such therapies, along with regular screening for latent TB infection (LTBI).

## 2. Case report

A 54-year-old male having a medical history of rheumatoid arthritis (RA) was admitted to the hospital due to experiencing symptoms of productive cough, fever, and night sweats over a period of one month. At the age of 48, he received a diagnosis of RA and was prescribed a treatment regimen consisting of sulfasalazine (SSZ) 500 mg once daily, methotrexate 15 mg weekly, folic acid 5mg weekly, and prednisolone 5mg daily. However, due to disease progression, he was started on tofacitinib 5mg twice daily for RA 6 weeks ago.

Upon examination, the patient exhibited a respiratory rate of 21 breaths per minute. Oxygen saturation while breathing normal air was measured at 91%. Auscultation revealed the presence of crepitations in both lungs. Blood examinations revealed a haemoglobin level of 11.6 g/dL, a white blood cell count of 4260 cells/$mm^3$, and a platelet count of 311,000 cells/$mm^3$. The erythrocyte sedimentation rate (ESR) was measured at 95 mm/h, and the concentration of C-reactive protein (CRP) was found to be 90 mg/L. Renal and liver function tests yielded normal results, as did the urinalysis.

The patient was started on a broad-spectrum antibiotic regimen, including amoxicillin-clavulanate and azithromycin, for suspected community-acquired pneumonia. However, his symptoms did not improve, and a chest X-ray was conducted following consultation with a pulmonologist, which revealed bilateral infiltrates in the upper lobes of the lungs. Multiple infiltrates were observed in the pulmonary region, specifically concentrated in the upper lobes. These infiltrates displayed characteristics such as consolidation, nodularity, and cavitation, indicating the presence of active tuberculosis pathology. On further questioning, the patient revealed having a history of TB infection 12 years ago. He was treated with 300 mg of isoniazid every day for 9 months and completed the treatment without any adverse effects.

His medical history was significant for latent tuberculosis (TB) infection, diagnosed based on a positive interferon-gamma release assay (IGRA) test. Further, he was receiving Tofacitinib, which carries a significant risk for LTBI reactivation. He had no other medical comorbidities and was a non-smoker with no history of substance abuse or alcohol consumption. He has been doing work from home for 10 months. There was no history of any contact with TB in the family or among close contacts. This strongly supports the final diagnosis of reactivation of latent tuberculosis infection following initiation of tofacitinib therapy.

The patient's sputum samples for acid-fast bacilli (AFB) were negative on two consecutive occasions. However, his Mantoux test was positive with an induration of 15 mm, and his interferon-gamma release assay (IGRA) was also positive. His $CD4^+$ T-cell count was normal, and his HIV rapid test was negative, further ruling out HIV infection.

After the Mantoux test was positive, Tofacitinib and methotrexate were discontinued, and he was started on standard four-drug anti-TB therapy (isoniazid 300mg, rifampicin 450mg, ethambutol 1200mg, and pyrazinamide 1500mg) under directly observed therapy. However, his RA symptoms worsened, and he developed joint pain and swelling. After consultation with his rheumatologist, methotrexate was restarted at a reduced dose of 10mg weekly, and hydroxychloroquine 200mg twice daily was added to his treatment regimen. Prednisolone was tapered off gradually. And as the patient was obese, he was advised to reduce weight to ease arthritis pain.

The patient experienced no significant complications of anti-TB therapy, but he did develop a mild skin rash with hydroxychloroquine, which resolved spontaneously. His RA symptoms improved with the addition of hydroxychloroquine, and he has been maintained on this combination therapy for RA. However, he was counselled about the need for careful monitoring for TB reactivation, and he was advised to avoid immunosuppressive therapies in the future.

## 3. Discussion

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis, which is highly transmissible and can pose a serious threat to health if not properly treated. While TB can affect any part of the body, pulmonary TB is the most frequently observed form. Latent TB infection (LTBI) occurs when the bacteria are dormant and do not produce any symptoms or signs of active TB disease. However, LTBI can become an active TB disease, especially in individuals with weakened immune systems, such as those receiving immunosuppressive therapies for autoimmune diseases like rheumatoid arthritis (RA).[7,9]

Tofacitinib is a Janus kinase inhibitor that was granted approval by the US Food and Drug Administration in 2012 as a treatment for RA. It has been demonstrated to effectively inhibit the signalling pathways of proinflammatory cytokines, which are important in the development of RA. However, the use of tofacitinib also suppresses the immune response, which raises the likelihood of infections, including TB.[10] As a result, the prescribing information for tofacitinib includes a boxed warning regarding the risk of severe infections, including TB.

Various clinical studies have shown that there is an increased chance of TB reactivation in individuals with rheumatoid arthritis who are administered tofacitinib.[2,7,11] According to a thorough analysis of randomized controlled trials, the occurrence of TB was found to be greater among those who were prescribed tofacitinib than those who were given a placebo or other types of DMARDs.[8,12,13] This case report confirms the observation that the risk of TB reactivation is higher among individuals with a history of latent TB infection.

The discussion surrounding tuberculosis (TB) infection and recurrence in rheumatoid arthritis (RA) patients treated with immunosuppressants extends beyond JAK Inhibitors. Studies have indicated that TNF inhibitors, such as infliximab, etanercept, and adalimumab, carry an increased risk of TB reactivation. Furthermore, other immunosuppressive agents like corticosteroids, including prednisone and methylprednisolone, as well as disease-modifying antirheumatic drugs (DMARDs) like methotrexate and leflunomide, have been associated with TB recurrence. Biologic DMARDs, including rituximab and abatacept, have also been implicated in TB reactivation. These findings

emphasize the importance of careful monitoring and proactive screening for TB in RA patients receiving immunosuppressive therapy, particularly those on TNF inhibitors or other agents that may compromise the immune response.[14,15]

The recurrence of tuberculosis (TB) in patients with rheumatoid arthritis (RA) is influenced by multiple factors. Firstly, immunosuppressive therapies used in the management of RA, such as corticosteroids and disease-modifying antirheumatic drugs, can compromise the immune system's ability to control Mycobacterium tuberculosis infection. Additionally, the presence of comorbidities, such as diabetes mellitus and chronic kidney disease, may increase the risk of TB recurrence in RA patients.[16] Furthermore, inadequate adherence to anti-TB medication and incomplete treatment courses can lead to treatment failure and subsequent recurrence. Close monitoring of RA patients receiving immunosuppressive therapies, diligent management of comorbidities, and comprehensive adherence to anti-TB treatment are crucial in minimizing the risk of TB recurrence in this population. Further research is needed to better understand the interplay between RA, immunosuppressive therapies, and TB recurrence, thus informing more effective preventive strategies.[17]

Diagnosing TB in RA patients can be challenging due to atypical presentations, particularly in those with underlying immunosuppression.[18] The patient had been experiencing symptoms of productive cough, fever, and night sweats for a month and was initially treated with broad-spectrum antibiotics for suspected community-acquired pneumonia but did not respond to the treatment. This highlights the significance of considering TB as a potential diagnosis in RA patients with a history of LTBI who present with respiratory symptoms.

Prompt diagnosis and management of active TB are crucial in RA patients to prevent complications, such as disseminated TB, which can be fatal in immunocompromised patients. The standard therapy for active TB is a combination of four drugs: isoniazid, rifampin, pyrazinamide, and ethambutol. In patients receiving tofacitinib, discontinuation of the drug is recommended until the TB is treated and resolved. The use of other DMARDs, such as methotrexate, may also need to be temporarily discontinued due to their immunosuppressive effects.[19] The Centres for Disease Control and Prevention (CDC) recommends initiating treatment for latent tuberculosis infection (LTBI) with isoniazid before starting immunosuppressive therapies. Testing for TB infection is also advised for individuals at increased risk, including those receiving immunosuppressive therapies such as TNF-alpha antagonists, systemic corticosteroids $\geq$15 mg prednisone/day, or immunosuppressive drugs after organ transplantation. Decisions on prophylactic measures should be individualized, considering patient attributes, preferences, and the risk of TB disease progression.[20–22]

In support of our findings, recent studies have provided further evidence in the field. Notably, van Vollenhoven et al. conducted a study to investigate the incidence of Pulmonary Tuberculosis (TB) in rheumatoid arthritis (RA) patients receiving tofacitinib compared to adalimumab. The results of this study revealed a significantly higher risk of tuberculosis in the tofacitinib group when compared to the adalimumab group.[23] Similarly, Winthrop et al. conducted an extensive analysis focusing on the risk of opportunistic infections (OIs) in RA patients treated with tofacitinib, and their findings corroborated an elevated risk of TB reactivation. Among the OIs reported, tuberculosis was the most prevalent.[24] These findings indicate an increased susceptibility to OIs in RA patients using tofacitinib, thereby emphasizing the criticality of vigilant monitoring and timely diagnosis within this specific patient population.

Comparing our findings to the existing literature, a consistent pattern emerges, demonstrating an augmented risk of TB infection in RA patients treated with tofacitinib. The significance of monitoring TB reactivation in individuals with RA who undergo immunosuppressive therapies is underscored by the present case report. This monitoring process should include screening for latent tuberculosis infection (LTBI) before initiating immunosuppressive therapies, such as tofacitinib, as well as ongoing evaluation of TB symptoms during the course of treatment. The American College of Rheumatology recognizes the importance of LTBI screening in all RA patients before commencing biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs), including tofacitinib. Furthermore, it is recommended to treat LTBI before initiating these specific therapies.[13] The prevention of TB reactivation in immunosuppressed RA patients holds utmost significance, as it serves to avert unfavourable outcomes associated with this condition.

## 4. Conclusion

In conclusion, this case report highlights the heightened risk of latent tuberculosis (TB) reactivation in rheumatoid arthritis (RA) patients undergoing tofacitinib treatment, underscoring the necessity for increased vigilance within the medical community. Given the potential for drug interactions, meticulous monitoring is essential when managing TB in RA patients receiving immunosuppressive therapies. Therefore, it is recommended to screen for latent TB infection (LTBI) before initiating such treatments in RA patients. Additionally, clinicians should consider implementing appropriate prophylactic measures, such as administering isoniazid, in patients with evidence of LTBI prior to initiating tofacitinib. These recommendations aim to minimize the risk of tuberculosis reactivation and enhance patient safety during tofacitinib therapy for RA. By adhering to these guidelines and advancing our understanding of this potential risk, clinicians can optimize the management and outcomes of RA patients while minimizing the risk of tuberculosis reactivation.

## Authors contribution

All authors have contributed equally in writing the manuscript.

## Patient/guardian consent for publication

Written informed consent was obtained from our patient for publication of this case report.

## Institutional ethical committee approval

Not Applicable.

## Standard for reporting

The study followed the CARE guidelines.

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## Declaration of competing interest

The authors declare no conflict of interest, financial or otherwise.

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