



doi • 10.5578/tt.2025031095
Tuberk Toraks 2025;73(3):227-230
Received: 28.03.2025 • Accepted: 04.05.2025

CASE REPORT

Disseminated tuberculosis despite preventive treatment in patients treated with tumor necrosis factor inhibitors: A report of two cases

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ABSTRACT

Disseminated tuberculosis despite preventive treatment in patients treated with tumor necrosis factor inhibitors: A report of two cases

Tumor necrosis factor-alpha inhibitors are widely used for autoimmune diseases but are associated with an increased risk of active tuberculosis due to impaired granuloma formation. Despite screening and preventive treatment for *Mycobacterium tuberculosis* before initiating therapy, risk persists, especially in endemic regions. Herein, it was aimed to report two cases of disseminated tuberculosis in patients treated with tumor necrosis factor-alpha inhibitors, despite completing preventive therapy. The first patient, a 34-year-old male with rheumatoid arthritis, developed miliary tuberculosis one month after starting adalimumab, despite prior isoniazid prophylaxis. The second patient, a 25-year-old female with ulcerative colitis, presented with miliary tuberculosis and elevated liver enzymes after receiving infliximab and completing preventive therapy. Both patients were treated with first-line anti-tuberculosis drugs, showing clinical, radiological, and bacteriological improvement. These cases underscore that immunosuppression caused by infliximab and adalimumab may overcome prophylactic protection, highlighting the need for continuous monitoring as preventive therapy does not guarantee complete protection.

Key words: Case report; tuberculosis miliary; antibiotic prophylaxis; tumor necrosis factor inhibitors

ÖZ

Tümör nekroz faktörü inhibitörleri ile tedavi edilen hastalarda koruyucu tedaviye rağmen dissemine tüberküloz: İki olgu sunumu

Tümör nekroz faktör-alfa inhibitörleri, otoimmün hastalıkların tedavisinde yaygın olarak kullanılmaktadır. Ancak, granülom oluşumunun bozulması nedeniyle aktif tüberküloz riski artmaktadır. Tedaviye başlamadan önce *Mycobacterium tuberculosis* için tarama yapılmasına ve önleyici tedavi uygulanmasına rağmen, özellikle endemik bölgelerde risk devam etmektedir. Tümör nekroz faktör-alfa inhibitörleri ile tedavi edilen ve önleyici tedavisi

Cite this article as: Rentería-Gómez R, Cinencio-Chavez WR, Zaragoza-Calderón CM, Laniado-Laborin R. Disseminated tuberculosis despite preventive treatment in patients treated with tumor necrosis factor inhibitors: A report of two cases. *Tuberk Toraks* 2025;73(3):227-230.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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tamamlanmış iki dissemine tüberküloz vakasını rapor ediyoruz. İlk hasta, romatoid artritli olan 34 yaşında bir erkek olup adalimumab tedavisine başladıktan bir ay sonra -daha önce izoniazid profilaksisi almış olmasına rağmen- miliyer tüberküloz geliştirmiştir. İkinci hasta ise ülseratif koliti olan 25 yaşında bir kadındır; infliksimab tedavisini aldıktan ve önleyici tedaviyi tamamladıktan sonra, miliyer tüberküloz ve yükselmiş karaciğer enzimleri ile başvurmuştur. Her iki hasta da birinci basamak anti-tüberküloz ilaçları ile tedavi edilerek klinik, radyolojik ve bakteriyolojik olarak iyileşme göstermiştir. Bu vakalar, infliksimab ve adalimumab tedavisinin oluşturduğu immünsupresyonun profilaktik tedaviyi aşabileceğini vurgulamakta; önleyici tedavinin tam koruma sağlamadığını göstererek sürekli izlemin gerekliliğine dikkat çekmektedir.

Anahtar kelimeler: Olgu raporu; miliyer tüberküloz; antibiyotik profilaksisi; tümör nekroz faktörü inhibitörleri

INTRODUCTION

Therapy with tumor necrosis factor-alpha inhibitors (TNFi) has revolutionized the management of autoimmune diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). However, it is well documented to increase the risk of active tuberculosis (TB) as they interfere with the formation and maintenance of granulomas during the infection (1). Therefore, it is essential to screen for TB infection in patients before initiating biological therapy and to administer preventive treatment when indicated (2).

Despite preventive treatment, the risk of developing active TB in patients on TNFi treatment persists, especially in regions with a high prevalence of TB (3). Herein, we aimed to describe two cases of patients with RA and ulcerative colitis (UC) who, after receiving preventive treatment against TB, developed disseminated TB following initiation of biological therapy. All patients included in this case report signed informed consent, ensuring their understanding and agreement to participate.

Case presentation

Case 1

A 34-year-old male with 20 years of RA received multiple treatments, including methotrexate, sulfasalazine, and systemic corticosteroids. However, due to inadequate therapeutic response and worsening RA symptoms, treatment with adalimumab (Humira®) was planned. The QuantiFERON®-TB Gold In-Tube Test was positive while the chest X-ray was normal. Preventive treatment for TB was initiated with daily isoniazid 300 mg for six months.

After completing preventive treatment, the patient began adalimumab therapy. One month later, he developed a fever and productive cough, predominantly at night. A chest X-ray revealed a miliary process, which was confirmed by computed tomography (Figure 1).

A rapid molecular sputum test (Xpert® MTB/RIF Ultra Cepheid) detected the *M. tuberculosis* complex (low load) without mutations in the *rpoB* (RNA polymerase beta subunit) gene, indicating no rifampicin resistance. The patient started first-line drug regime (rifampicin, isoniazid, pyrazinamide and ethambutol), with excellent clinical response.

Case 2

A 25-year-old female, diagnosed six years earlier with UC, had poor response to treatment with mesalazine and systemic steroids. She underwent a TB infection screening, which showed a positive tuberculin skin test (TST) and a normal chest X-ray. Preventive therapy with isoniazid (300 mg/day) was started, and after 10 weeks of treatment, she received the first dose of infliximab, completing the induction phase six weeks later. Later on, she completed a six-month isoniazid regimen.

Two weeks after the maintenance dose of infliximab, she developed fever, diaphoresis, cough, asthenia and lost six kg. A chest X-ray showed a miliary pattern and subsegmental atelectasis of the left lower lobe (Figure 2). A rapid molecular sputum test (Xpert® MTB/RIF Ultra Cepheid) detected *M. tuberculosis* complex with trace load and indeterminate

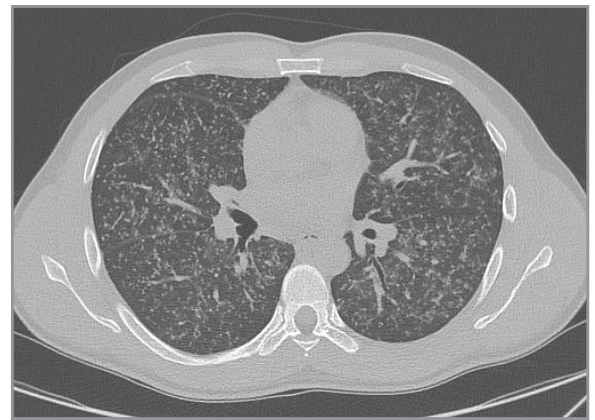


Figure 1. CT scan of the thorax showing a uniformly distributed miliary pattern.

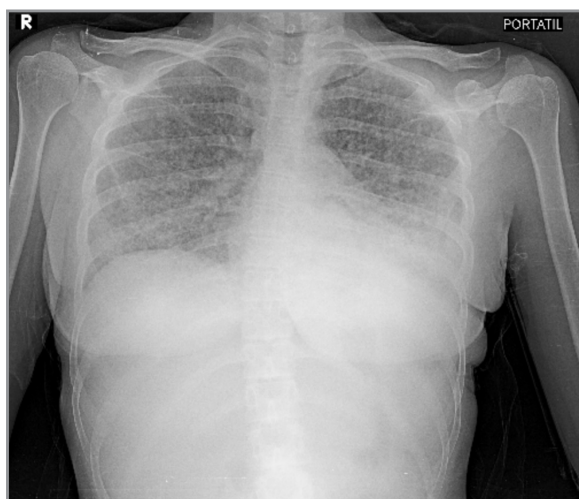


Figure 2. Chest X-ray showing a uniformly distributed miliary pattern and left pleural effusion.

resistance to rifampicin (a culture from the same sputum sample was later reported as negative). Blood work showed significantly elevated liver enzymes: Alkaline phosphatase= 2.326 U/L, gamma-glutamyl-transferase= 826 U/L, and lactate dehydrogenase= 562 U/L.

Despite these findings, treatment for active TB was started with a first-line drug regimen. The patient was hospitalized for 20 days due to respiratory distress, which did not require mechanical ventilation. Subsequently, treatment dosage was adjusted per weight gain. Although she showed an excellent clinical response, liver enzymes progressively decreased without returning to normal.

DISCUSSION

Active TB is a significant complication in patients treated with TNFi, especially in endemic regions. This

evidence underlines the importance of screening for TB and its treatment before starting biological therapy, a routine practice to mitigate this risk. The risk of developing active TB increases fourfold once treatment with TNFi begins, although the incidence varies according to the drug selected (Table 1) (4). Infliximab and adalimumab are the agents most frequently associated with the development of active TB (2). These were the drugs administered to the patients in this report.

In the study by Jung et al., in 2022, conducted in South Korea with 4.736 patients with RA, 14 (1.19%) cases of active TB were documented among the 1.168 patients who completed prophylaxis (5). Lee et al., in 2021, analyzed 1.434 patients with IBD treated with TNFi agents, of whom 166 received prophylaxis; 3 (1.80%) patients developed active TB despite receiving preventive therapy (6). These results suggest that TB preventive treatment might reduce the risk of active disease but not eliminate it.

Although preventive treatment with isoniazid has proven effective in reducing the risk of active TB, its efficacy may be limited by factors such as adherence to the regimen and the increasing emergence of isoniazid-resistant strains in settings where TB is endemic (7-9). In addition, the immunosuppression caused by TNFi, especially infliximab and adalimumab, can overcome the protection conferred by prophylaxis.

Both patients showed favorable progress with the primary anti-TB treatment. Clinically, respiratory symptoms resolved; follow-up imaging studies show resolution of the miliary pattern, and sputum cultures are negative.

Table 1. Biological therapies, tuberculosis risk and the need for preventive therapy

Target	Generic name	Indication	TB risk	Preventive therapy
TNF	Infliximab	RA, PsoA, SpA, Pso, CD, UC	High	Yes
	Adalimumab	RA, PsoA, SpA, Pso, CD, UC, JIA	High	Yes
JAKs	Tofacitinib	RA, PsoA, UC	High	Yes
IL 12/23	Ustekinumab	PsoA, Pso, UC	Low	Yes
Integrin	Vedolizumab	CD, UC	Low	Yes
CD20	Rituximab	RA, GPA, MPA	No	No

TB: Tuberculosis, TNF: Tumor necrosis factor, IL: Interleukin, JAKs: Janus kinase inhibitor, RA: Rheumatoid arthritis, PsoA: Psoriatic arthritis, SpA: Spondyloarthritis, Pso: Psoriasis, CD: Crohn's disease, UC: Ulcerative colitis, JIA: Juvenile idiopathic arthritis, MPA: Microscopic polyangiitis, GPA: Granulomatosis with polyangiitis.

*Adapted from Rath, 2022 (4).

The cases described highlight that the risk of developing active TB in patients treated with TNFi persists despite receiving TB preventive treatment. In endemic areas with high rates of TB infection due to community transmission, this risk is higher, underlining the need for close monitoring even after preventive treatment is completed since it does not guarantee total protection in immunosuppressed patients.

PATIENT CONSENT

Patient consent was obtained.

CONFLICT of INTEREST

The authors have no conflict of interest to declare.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: RRG, RLL

Analys/Interpretation: RRG, RLL, WRCC

Data acquisition: RRG, WRCC, CMZC

Writing: RRG, WRCC, CMZC

Clinical Revision: RRG, CMZC, RLL

Final Approval: RLL

REFERENCES

1. Robert M, Miossec P. Reactivation of latent tuberculosis with TNF inhibitors: Critical role of the beta 2 chain of the IL-12 receptor. *Cell Mol Immunol* 2021; 18: 1644-51. <https://doi.org/10.1038/s41423-021-00694-9>
2. Dobler CC. Biologic agents and Tuberculosis. *Microbiol Spectr* 2016; 4(6). <https://doi.org/10.1128/microbiolspec.TNMI7-0026-2016>
3. Chaer FGG, de Lucena Valim JM, Reis RC, Klautau GB, de Souza BDB. Use of biologic agents and risk of tuberculosis in Brazil, a tuberculosis high-burden country. *Drugs Context* 2020; 9: 1-7. <https://doi.org/10.7573/dic.212598>
4. Rath E, Bonelli M, Duftner C, Gruber J, Mandl P, Moazed-Furst F, et al. National consensus statement by the Austrian Societies for Rheumatology, Pulmonology, Infectiology, Dermatology and Gastroenterology regarding the management of latent tuberculosis and the associated utilization of biologic and targeted synthetic disease modifying antirheumatic drugs (DMARDs). *Wien Klin Wochenschr* 2022; 134: 751-65. <https://doi.org/10.1007/s00508-022-02062-7>
5. Jung SM, Han M, Kim EH, Jung I, Park YB. Comparison of developing tuberculosis following tumor necrosis factor inhibition and interleukin-6 inhibition in patients with rheumatoid arthritis: A nationwide observational study in South Korea, 2013-2018. *Arthritis Res Ther* 2022; 24: 157. <https://doi.org/10.1186/s13075-022-02842-6>
6. Lee JY, Oh K, Hong HS, Kim K, Hong SW, Park JH, et al. Risk and characteristics of tuberculosis after anti-tumor necrosis factor therapy for inflammatory bowel disease: A hospital-based cohort study from Korea. *BMC Gastroenterol* 2021; 21(1): 390. <https://doi.org/10.1186/s12876-021-01973-5>
7. Rangaka MX, Hamada Y, Duong T, Bern H, Calvert J, Francis M, et al. Evaluating the effect of short-course rifapentine-based regimens with or without enhanced behaviour-targeted treatment support on adherence and completion of treatment for latent tuberculosis infection among adults in the UK (RID-TB: Treat): Protocol for an open-label, multicentre, randomised controlled trial. *BMJ Open* 2022; 12(9): e057717. <https://doi.org/10.1136/bmjopen-2021-057717>
8. Li TL, Chan TH, Wang CH, Jou R, Yu MC, Putri DU, et al. Acquired resistance to isoniazid during isoniazid monotherapy in a subject with latent infection following household rifampicin-resistant tuberculosis contact: A case report. *Infect Drug Resist* 2021; 14: 1505-9. <https://doi.org/10.2147/IDR.S304799>
9. Dookie N, Ngema SL, Perumal R, Naicker N, Padayatchi N, Naidoo K. The changing paradigm of drug-resistant tuberculosis treatment: Successes, pitfalls, and future perspectives. *Clin Microbiol Rev* 2022; 35(4): e0018019. <https://doi.org/10.1128/cmr.00180-19>