

Case Report

Tuberculosis-associated IRIS in a young non-HIV patient undergoing TNF- α blockade for ankylosis spondylitis: a rare case report from Italy

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ABSTRACT

Patients receiving anti-TNF- α therapy are at increased risk of developing tuberculosis (TB). While immune reconstitution inflammatory syndrome (IRIS) is classically associated with HIV-infected individuals initiating antiretroviral therapy, it has also been reported in HIV-negative patients following the initiation of anti-tubercular treatment. We present a case of a non-HIV patient who developed IRIS after being diagnosed with TB while on anti-TNF- α therapy. The optimal management of IRIS in this setting remains unclear, although corticosteroids have been used with varying success. Some authors suggest that continuation of anti-TNF- α agents during IRIS may be beneficial. Our case highlights the diagnostic and therapeutic challenges in managing TB-IRIS in non-HIV patients and the need for further research in this population.

1. Introduction

Ankylosing spondylitis (AS) is a chronic and progressive inflammatory joint disease primarily affecting the spine and pelvis, leading to persistent inflammation, stiffness, and pain. A dysregulated immune response, characterized by the overproduction of proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-17 (IL-17), plays a central role in the pathogenesis of AS. Biologic drugs, targeting these mediators, particularly TNF- α -inhibitors, have become a cornerstone in the management of AS [1]. Despite their proven efficacy, TNF- α inhibitors are associated with an increased risk of serious infections, most notably tuberculosis (TB). A recent systematic review reported that anti-TNF- α therapy is associated with a significantly higher risk of infectious adverse events (AEs), with a 20% increase in infections, 40% increase in serious infections, and 250% higher incidence of tuberculosis [2]. According to international rheumatology guidelines, screening for TB infection is part of the patient's evaluation before initiation of immunomodulating treatments, including anti-TNF- α agents [3]. Despite this established screening approach, and the indication to start TB infection treatment before

immunomodulant treatments, no clear recommendation exists on how to monitor patients with an initial negative TB screening. Immune reconstitution inflammatory syndrome (IRIS) is a clinical phenomenon of immune-mediated inflammation against various microorganisms during recovery from immunosuppressed conditions. This phenomenon is well recognized in HIV-infected populations after initiation of antiretroviral treatment (ART), but it has been also recognized in HIV-negative immunocompromised patients [4]. Here we report a case of pulmonary tuberculosis complicated by IRIS in a young Italian patient treated with TNF- α inhibitor for AS.

2. The clinical case

In December 2024, a 35-year-old Caucasian male was admitted to the Infectious Diseases Department of Policlinico Tor Vergata in Rome, Italy, with a one-month history of cough, fever, weight loss, and night sweats. His medical history was notable for AS, for which he was undergoing treatment with adalimumab, a TNF- α inhibitor monoclonal antibody, administered every three weeks. In 2016, before initiation of adalimumab, he was screened for TB infection using QuantiFERON-TB

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Gold test and was negative. Prior to this hospital admission, he was treated with several antibiotics including 10 days of ceftriaxone plus 7 days of clarithromycin, followed by 3 days of levofloxacin, without symptom improvement. During this admission, Computed Tomography-scan (CT) of the thorax revealed right lung parenchymal consolidation (figure 1A). Blood tests showed an elevated C-reactive protein (CRP) level (28 mg/L), with normal levels for procalcitonin (PCT) and white blood cell (WBC) count. Urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were negative, while the QuantiFERON-TB Gold test was positive, with TB antigen tube 1 (TB1) and TB antigen tube 2 (TB2) values of 3.42 IU/mL each and a mitogen control value of 3.42 IU/mL. Therefore, sputum examination was performed, resulting negative for *Mycobacterium tuberculosis* (MTB), both by molecular testing with polymerase chain reaction (PCR) using the Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA) and by microscopic examination for acid-fast bacilli (AFB). Empirical antibiotic therapy was started with cefepime (2,000 mg every 8 h) and doxycycline (100 mg every 12 h). After a week of treatment, the patient's condition did not improve, so a bronchoscopy with bronchoalveolar lavage (BAL) was performed. PCR test using Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA) on BAL sample detected *Mycobacterium tuberculosis* complex while microscopic examination was negative for AFB. Additionally, MTB was identified in the patient's stool samples through PCR analysis performed using the Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA). Rifampicin resistance genes were not detected by the molecular assay. A total body CT scan excluded extra-pulmonary TB. First-line antitubercular therapy using rifampicin (600 mg daily), isoniazid (300 mg daily), ethambutol (1,200 mg daily), and pyrazinamide (1,500 mg daily) was promptly initiated and, after excluding any adverse event, the patient was discharged home in good clinical conditions. Adalimumab therapy for AS was discontinued (last dose administered in November 2024); the patient experienced a worsening of AS symptoms, managed with daily ibuprofen and sulfasalazine. In March 2025, two months after hospital discharge, the patient returned to the emergency department presenting again with cough, weight loss, night sweats and persistent fever. A thoracic CT revealed a marked progression of pulmonary consolidations (Fig. 1B) and the appearance of lymphadenopathy with central necrosis in the right retro clavicular and paratracheal lymph nodes. Blood tests showed a high CRP level (100.40 mg/L), while PCT and WBC counts were within normal ranges. An additional bronchoscopy with BAL was performed, suspecting either TB treatment failure or a superinfection. Microbiological analysis detected the presence of *Mycobacterium tuberculosis* complex by the Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA) and *Aspergillus* spp. DNA by real-time PCR (Fungiplex® *Aspergillus* assay, Bruker Daltonics, Bremen, Germany); fungal cultures and galactomannan testing were negative. Ziehl-Neelsen staining of BAL sample was negative for AFB and *Mycobacterium tuberculosis* culture was negative. Molecular drug susceptibility testing was performed using the Anyplex™ MTB/MDR/XDR Detection assay (Seegene, South Korea), showing no resistance to first- or second-line anti-tubercular drugs. Based on these findings, the ongoing antitubercular regimen was continued, and empirical anti-fungal therapy with liposomal amphotericin B (3 mg/kg) was initiated. Liposomal amphotericin B was administered empirically and subsequently discontinued after invasive pulmonary aspergillosis was definitively ruled out, based on negative fungal cultures for *Aspergillus* spp., negative galactomannan testing on BAL samples, and thoracic CT findings not typical of the disease. To investigate other potential concomitant conditions, such as hematologic malignancy, a PET-CT scan was performed, demonstrating increased glucose uptake in the right retro-clavicular and paratracheal lymph nodes. Additionally, increased metabolic activity was observed in the right upper and middle lung lobes with a maximum Standardized Uptake Value (SUVmax) of 13.3. Increased glucose uptake was also detected in a lymph node in the Baretz region showing an SUVmax of 9.5. Surgical excision of the right retro clavicular lymph node was performed and its histopathological

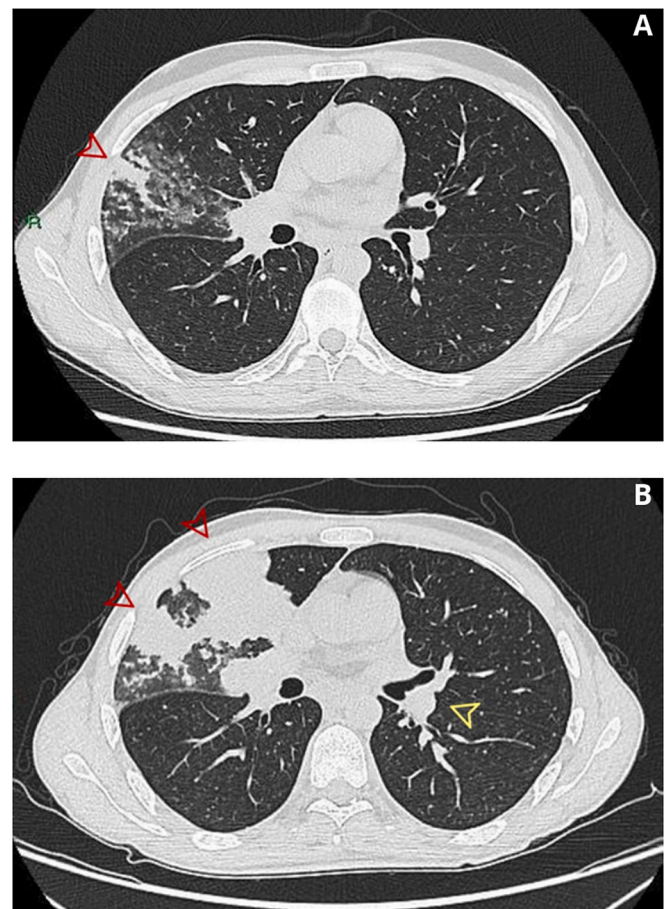


Fig. 1. CT-scan comparison. **Panel A** shows parenchymal consolidation in the right upper lobe and the middle lobe (red arrow). **Panel B** demonstrates progression and increased extent of the previously noted pulmonary consolidation (red arrows) and hilar lymphadenopathy (yellow arrow).

examination (Figs. 2-3) showed chronic granulomatous necrotizing lymphadenitis, compatible with lymph node localization of TB. PCR performed on the lymph node specimen (INNO-LiPA *Mycobacteria* assay, Fujirebio, Ghent, Belgium) was also positive for *Mycobacterium tuberculosis*. The patient was diagnosed with possible Immune Reconstitution Inflammatory Syndrome (IRIS) secondary to tuberculosis treatment, supported by worsening lobar consolidation and the emergence of a pathological lymph node approximately eight weeks after initiation of anti-tubercular therapy. Although corticosteroid therapy

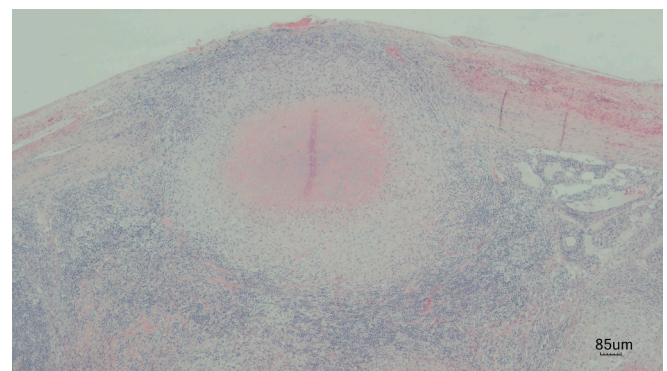


Fig. 2. Histologic examination of the lymph node. Representative microscopic picture of lymph node showing a characteristic necrotizing granuloma (original magnification 4x, hematoxylin-eosin stain).

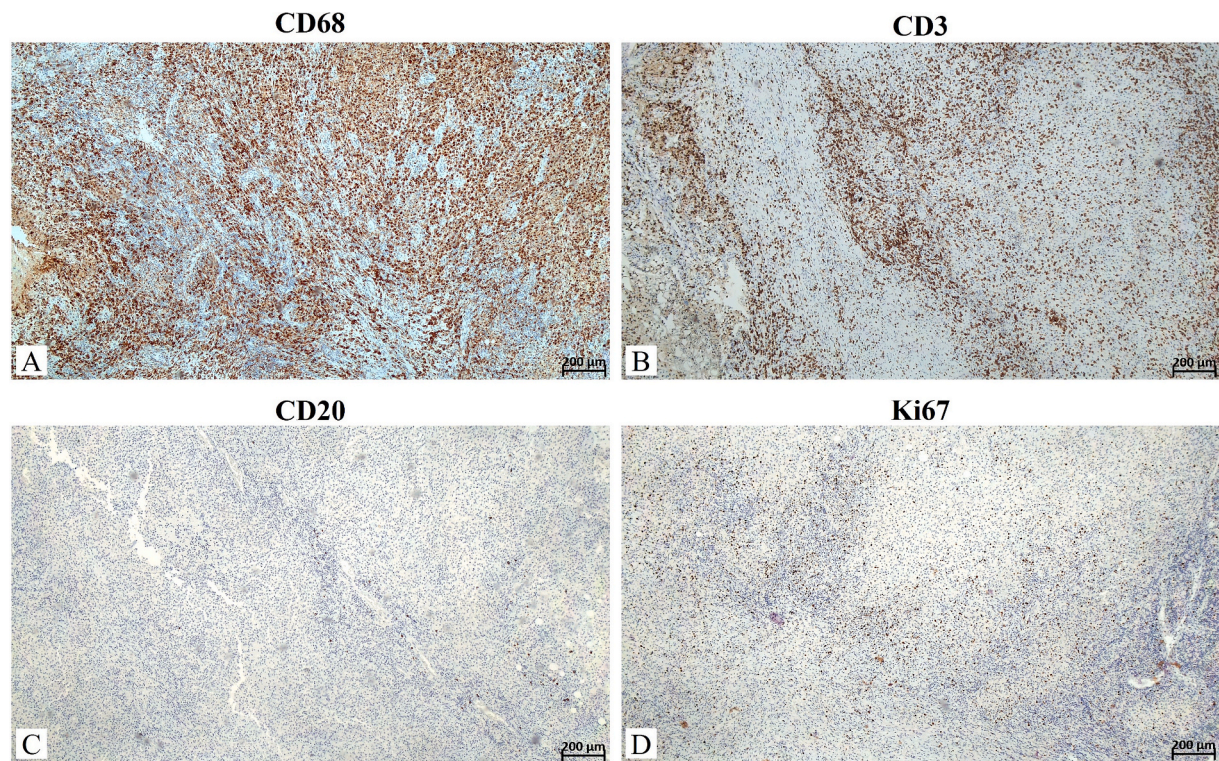


Fig. 3. Immunohistochemical staining of the supraclavicular lymph node biopsy. **Panel A:** CD68 immunostaining highlights a dense infiltrate of macrophages within the granulomatous areas. **Panel B:** CD3 staining shows a rich population of T lymphocytes, particularly at the periphery of granulomas. **Panel C:** CD20 staining demonstrates rare B lymphocytes. **Panel D:** Ki-67 immunostaining reveals scattered proliferating cells, indicating a low overall proliferative index. Magnification 5× Scale bar = 200 µm.

could be considered in such cases, no specific treatment for IRIS was initiated, as the patient demonstrated progressive clinical improvement with antitubercular therapy alone. Following a slow but steady clinical improvement, the patient was discharged home with instructions to maintain the current therapeutic regimen. The patient underwent regular outpatient follow-up and completed a total of nine months of anti-tubercular therapy, consisting of a four-drug regimen (rifampicin, isoniazid, ethambutol, pyrazinamide) for 6 months, and 2-drug regimen (rifampicin and isoniazid) for additional 3 months. Clinical symptoms progressively improved, with complete symptom resolution occurring approximately six months after initiation of anti-tubercular therapy. Follow-up chest CT scans performed in October 2025 and January 2026 (10 and 12 months after treatment initiation, respectively) demonstrated a marked reduction in mediastinal lymphadenopathy and significant improvement of right-sided pulmonary consolidations, supporting a favourable treatment outcome. As for AS, during follow-up rheumatologic evaluation contraindicated reintroduction of anti-TNF- α therapy hence treatment with sulfasalazine and ibuprofen was continued, and still ongoing.

3. Discussion

One of the major adverse events in people undergoing treatment with biologic agents such as TNF- α inhibitors is reactivation of TB infection [2]. In Europe and many other regions, screening for TB infection is strongly recommended before starting treatment with biologic agents, and TB infection treatment initiated, if indicated [5]. TB infection reactivation associated with anti-TNF- α drugs often presents atypically, with extrapulmonary and disseminated forms, causing a delay in diagnosis. Initial treatment response may be poor owing to the persistence of anti-TNF- α agents in the body, contributing to significant morbidity and increased mortality in affected patients [6]. In this clinical case, the patient had TB screening with a QuantiFERON-TB Gold test

prior to initiating adalimumab therapy and tested negative. However, no re-screening was performed thereafter, likely due to the lack of significant risk factors for TB exposure. The patient's ethnicity, prior negative QuantiFERON-TB Gold test and stable residence in Italy (a low TB endemic country), also contributed to the delayed diagnosis of TB infection. Considering the risk of TB infection reactivation during anti-TNF- α treatment, together with evolving global and local TB epidemiology, annual screening for TB infection would be desirable for all patients receiving such treatment, prompting early diagnosis and treatment. Additionally, tuberculosis should be considered among the differentials in the diagnostic workup for persistent fever in patients receiving immunomodulatory treatments with TNF- α inhibitors. In the present case, despite two months of effective anti-TB therapy, the patient developed worsening of both clinical and radiological features of TB. The histopathologic findings, on the subsequently excised lymph node, attributed the deterioration to a paradoxical reaction known as immune reconstitution inflammatory syndrome (IRIS). IRIS, commonly observed in individuals with HIV after starting ART, is characterized by a restoration of CD4 + T-cell counts that leads to an exaggerated immune response against pathogens and host tissues [7]. IRIS has also been described in HIV-negative patients with tuberculosis [8]. In HIV-negative patients, tuberculosis associated IRIS (TB-IRIS) may present with clinical deterioration (such as worsening of fever, cough or dyspnoea) or progression of primary lesions (including enlargement of lymph nodes, expansion of parenchymal lesions or development of pleural effusion) as well as with the emergence of new TB foci at local or distant sites [9]. According to the criteria proposed by Sueki et al., the diagnosis of non-HIV IRIS requires three key elements: the patient must be HIV-negative, recovering from an immunocompromised state, and must develop a new or worsening inflammatory condition triggered by antigens or pathogens that were already present before immune recovery. The diagnosis excludes cases where the flare is due to inappropriate treatment withdrawal, disease progression, or new infections acquired

after recovery [10]. In this case, the patient fulfilled these three criteria, hence the worsening of his symptoms during anti-TB treatment, was attributed to a TB-IRIS. The detection of *Aspergillus* DNA by PCR on BAL fluid was not considered sufficient to explain the clinical deterioration as both the galactomannan assay and the fungal culture were negative. Additionally, no radiological findings suggestive of pulmonary invasive aspergillosis were observed. Histological examination of the lymph node demonstrated chronic granulomatous necrotizing lymphadenitis, and PCR analysis of the lymph node tissue was positive for *Mycobacterium tuberculosis* DNA, further supporting the diagnosis of TB-IRIS. There are currently no standardized guidelines for the management of TB associated IRIS. Although only a few cases of severe paradoxical reactions have been reported in patients who developed tuberculosis during anti-TNF therapy, there is concern that discontinuation of the TNF- α inhibitor may heighten the risk of this complication [4]. Some authors have proposed the continuation or early reintroduction of TNF- α inhibitors, alongside antitubercular therapy, in cases of TB occurring during anti-TNF- α treatment [11]. Rivoisy et al. [12] reported that low-dose corticosteroids may be insufficient to prevent IRIS onset in this context, pointing out the potential role of anti-TNF- α reintroduction to manage severe IRIS manifestations and steroid refractory TB IRIS, as also reported in other cases [13,14]. Similarly, Tanaka et al. [15] suggested that continuing anti-TNF- α therapy may be effective in preventing the development of IRIS. Some patients' clinical condition improved with continuation of anti-TB therapy alone, while oral steroids may be required in patients with marked and progressive clinical or radiological worsening [9]. A recent review of case reports [5] suggests that high-dose corticosteroids and/or anti-TNF- α may be necessary in severe presentations of anti-TNF- α induced TB-IRIS. In contrast, milder cases often resolve spontaneously and may not require pharmacologic intervention. However, when treatment is used for mild cases, low to moderate doses of corticosteroids have generally proven effective [9]. In one randomized controlled trial, involving HIV positive outpatients with TB-IRIS beneficial effects were found to be similar to placebo [17]. On reviewing TB-IRIS management, it was noted that corticosteroids were not administered in approximately half of the cases, indicating that their use should be carefully considered. Hence, decisions regarding the initiation, dosage, and duration of corticosteroid therapy should be made on an individualized, case-by-case basis [16]. This body of evidence is largely based on case reports and small observational studies. To date, no controlled clinical trials have been conducted to support this approach. In the clinical case presented here, steroids were not used, as the patient's clinical condition improved with continuing TB treatment.

4. Conclusion

Tuberculosis screening is critical for all patients prior to initiating anti-TNF- α therapy. Given the elevated risk of TB reactivation and progression in this population, annual TB screening should be considered even in the absence of overt risk factors for TB exposure. In patients presenting with persistent respiratory symptoms and fever, active TB must be included in the differentials. If diagnosed, patients should be closely monitored throughout treatment due to the potential development of TB-IRIS. Current evidence on the optimal management of active TB in patients receiving TNF- α inhibitors remains limited. The available studies suggest that abrupt discontinuation of immunosuppressive therapy may not be advisable, as it could increase the risk of IRIS. Corticosteroids may be beneficial in cases of progressive clinical or radiological deterioration, whereas continuation of anti-tubercular therapy alone may suffice in patients with mild TB-IRIS manifestations. Further research is necessary to establish clear management guidelines in this complex clinical setting.

5. Data statement

Data sharing is not applicable to this article as it involves individual

patient data that are subject to privacy restrictions.

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Ethical statement

The authors confirm that written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required for this type of study, in accordance with local legislation and institutional requirements.

CRediT authorship contribution statement

Enrico Perugini: Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Laura Campogiani:** Writing – review & editing, Writing – original draft, Investigation. **Luigi Coppola:** Writing – review & editing. **Federico Cecilia:** Writing – review & editing. **Sara Ciarpaglini:** Writing – review & editing. **Martina Leone:** Writing – review & editing. **Manuel Scimeca:** Writing – review & editing, Investigation. **Amedeo Ferlosio:** Writing – review & editing, Investigation. **Vincenzo Malagnino:** Writing – review & editing. **Marco Iannetta:** Writing – review & editing, Writing – original draft, Supervision. **Loredana Sarmati:** Writing – review & editing, Validation, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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