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A 24-YEAR-OLD MAN WITH DISSEMINATED TUBERCULOSIS AND A CORTICOSTEROID-REFRACTORY PARADOXICAL REACTION TO ANTI-TUBERCULOUS TREATMENT

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ABSTRACT

Introduction: Paradoxical reactions during anti-tuberculosis treatment are immune-mediated reactions that complicate treatment even in immunocompetent patients.

Case description: We present the case of a previously healthy 24-year-old man with disseminated tuberculosis, who experienced persistent fever, weight loss, and radiological deterioration despite appropriate treatment. These findings were consistent with a paradoxical reaction to treatment, after extensive work-up excluded treatment failure, co-infections, and systemic inflammatory conditions. However, high-dose corticosteroids failed to achieve improvement. Ultimately, an interleukin-1 receptor antagonist (anakinra) was initiated as a salvage therapy for this corticosteroid-refractory paradoxical reaction, resulting in rapid defervescence, normalization of inflammatory markers, and radiological improvement.

Conclusion: This case underscores the diagnostic and therapeutic challenges when managing severe reactions in tuberculosis patients, while highlighting the importance of biologics like anakinra in corticosteroid-refractory paradoxical reactions.

KEYWORDS

Tuberculosis, paradoxical reaction, corticosteroids, anakinra

LEARNING POINTS

- Paradoxical reactions to anti-tuberculosis treatment remain an overlooked cause of non-resolving fever in immunocompetent and immunocompromised patients with tuberculosis and should be considered after ruling out treatment-refractory or complicated infection in persistently febrile patients.
- Prompt treatment of severe reactions prevents major complications and improves clinical outcomes.
- Corticosteroid-refractory paradoxical reactions illustrate the potential role of biologics, such as tumour necrosis factor inhibitors and, in our case, interleukin-1 receptor antagonists, in controlling excessive inflammation in tuberculosis.

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INTRODUCTION

Paradoxical reactions (PRs) to anti-tuberculosis treatment (ATT) have an estimated frequency of up to 23% in human immunodeficiency virus (HIV)-negative patients[1]. Defined as deterioration of pre-existing lesions or development of new lesions during ATT, they are mediated by a treatment-triggered excessive inflammatory response against increased mycobacterial antigenic load and are driven by reversal of pre-existing immunosuppression. High bacillary load may indicate severe - yet potentially "reversible" by treatment - immune exhaustion. PRs cannot be neither accurately predicted nor efficiently prevented, and no standard treatment algorithm has been proposed. When clinical response to high-dose corticosteroids is inadequate, guidelines on how to use biologics are completely lacking, necessitating individualized clinical judgement, as highlighted by our case.

CASE DESCRIPTION

A previously healthy 24-year-old man presented to the Emergency Department of a tertiary hospital in Athens, Greece, reporting fever during the last week, accompanied by fatigue, shortness of breath, night sweats, and unintentional weight loss (20 kg during the last year). He was of Indian origin, had been in Greece for three years, and resided in the centre of Athens while working at a fast-food restaurant. He was a former smoker and did not consume alcohol or illicit drugs.

Upon presentation, he appeared unwell and cachectic, was febrile and well-oriented without any neurological symptoms, and required low-flow supplemental oxygen. Auscultation revealed non-musical crackles bilaterally. Laboratory results included increased C-reactive protein (130 mg/l), leucocytosis with neutrophilic predominance, anaemia (haemoglobin: 9 g/dl), hyperferritinaemia (925 ng/ml), and hyponatremia (125 mmol/l). Computed tomography pulmonary angiogram (CTPA) ruled out pulmonary embolism and confirmed cavitary lesions in the left lung apex, alongside innumerable millimetric centrilobular nodules with tree-in-bud morphology, as well as mild pleural effusions bilaterally *(Fig. 1A)*. Attempts to obtain sputum samples were unsuccessful, so a diagnostic bronchoscopy was performed, and a well-tolerated standard four-drug ATT regimen (isoniazid, rifampicin, pyrazinamide, ethambutol) was started.

Serology testing for HIV, hepatitis B virus and hepatitis C virus was negative. Ziehl-Neelsen staining for acid-fast bacilli was positive in both bronchial secretions and bronchoalveolar lavage (BAL) fluid, molecular testing (GeneXpert MTB/RIF Ultra) confirmed the presence of rifampicin-susceptible *Mycobacterium tuberculosis*, and cultures were positive 15 days later. Abdominal computed tomography (CT) scan revealed hepatosplenomegaly, perihepatic and perisplenic free fluid, peritoneal lesions suggestive of tuberculous peritonitis, a hypodense lesion in the spleen, and intra-abdominal lymphadenopathy. Heart ultrasound ruled out pericardial effusion.

Due to non-resolving fever, persistent inflammatory syndrome and catabolic state while on uninterrupted ATT and despite the initial respiratory improvement, the patient was evaluated for other causes of persistent fever, while follow-up CT (day 20 of ATT) suggested deteriorating nodular lesions *(Fig.1B and C)* and intravenous methylprednisolone (1 mg/kg) was started. Imaging was not suggestive of difficult-to-treat musculoskeletal disease or empyema. Directly observed therapy by the nursing staff excluded lack of compliance. ATT malabsorption was also unlikely, given the absence of compatible findings, such as diarrhoea or bowel oedema. Drug resistance was not inferred by genotypic or phenotypic drug susceptibility testing. Ruling out drug fever warranted serial discontinuation of ATT components. Each drug was discontinued and reinstated after three days, without any changes in the fever pattern. Isoniazid-induced lupus remained a rare clinical scenario, characterized by strong antinuclear antibodies (ANA) positivity, but our patient did not present any lupus-like symptoms and was consistently ANA-negative. Pulmonary co-infections and systemic infections were repetitively excluded. Additional testing (serum β-D-glucan, Leishmania antigen in blood, peripheral

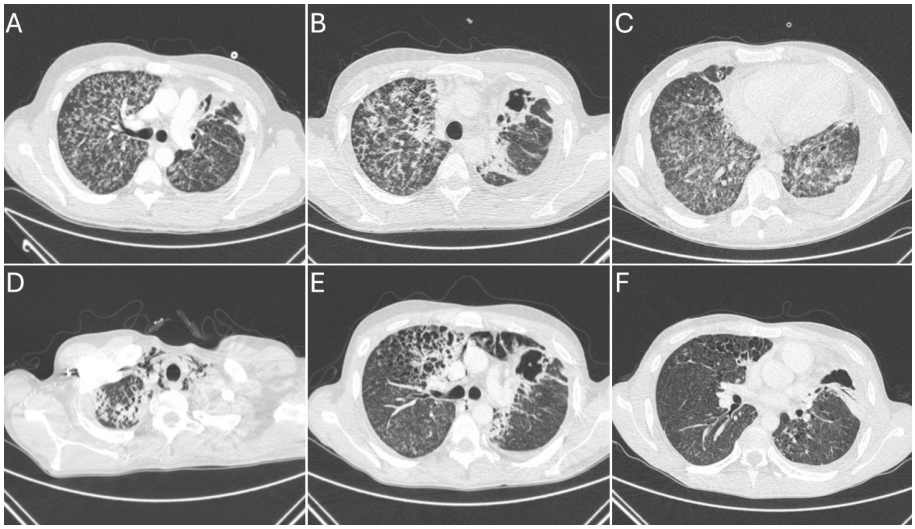


Figure 1. *Computed tomography pulmonary angiogram findings. A) Cavitary lesions in the apex of the left lung, alongside innumerable millimetric centrilobular nodules with tree-in-bud morphology in both lungs; B and C) Deteriorating nodular lesions; D and E) Small left-sided pneumothorax, pneumomediastinum and subcutaneous emphysema; F) Radiological improvement, albeit with extended fibrosis.*

blood smear for malaria) came back negative.

Respiratory deterioration warranted a repeat CT (day 35 of ATT), confirming non-severe pneumothorax, pneumomediastinum and subcutaneous emphysema, most likely due to rupture of an underlying bulla or cavitary lesion *(Fig. 1D and E)*. Conservative treatment with oxygen therapy led to marked improvement. A second diagnostic bronchoscopy was performed (day 45 of ATT), and all tests turned out negative, including negative BAL smear microscopy. Due to anaemia and slightly abnormal liver function tests, a liver biopsy was performed, ruling out secondary hemophagocytic lymphohistiocytosis, and revealing mild, non-specific, non-granulomatous lymphocytic portal inflammation.

A corticosteroid-refractory PR had been suspected before the completion of this diagnostic work-up, on a basis of non-improvement after administration of methylprednisolone (1 mg per kg) for approximately one month. Intravenous anakinra was initiated, at a dose of 300 mg daily, while slowly tapering corticosteroids. This led to rapid clinical and laboratory improvement. Fever subsided within one week, inflammation markers decreased, haematological parameters improved *(Fig. 2)*, and a repeat CT confirmed improvement, albeit with extended fibrotic damage to the lung parenchyma *(Fig. 1F)*. After 30 days, anakinra was reduced to 200 mg daily subcutaneously, and the patient was receiving 4 mg of methylprednisolone daily alongside rifampicin and isoniazid. He was discharged and regularly followed up as an outpatient.

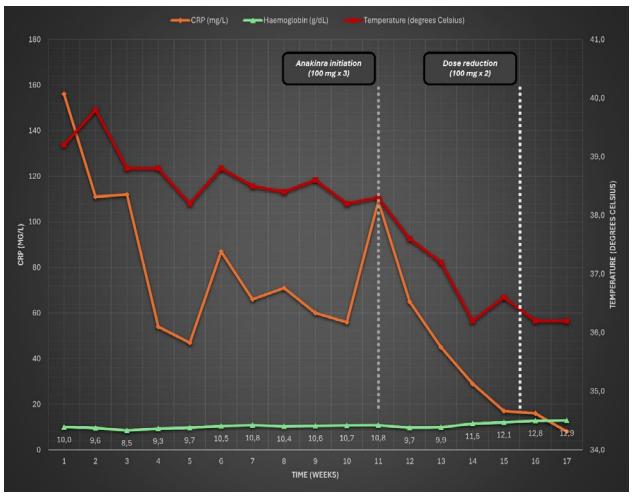


Figure 2. *Evolution of temperature, C-reactive protein (CRP) and haemoglobin values throughout treatment, emphasizing improvement after anakinra initiation. Grey dotted line: Anakinra initiation (day 70). White dotted line: Anakinra dose reduction (day 100).*

DISCUSSION

Fever in tuberculosis patients usually resolves by the second week of ATT, but few patients remain febrile for weeks or even months[2]. Although fever represents an evolutionarily beneficial immunological response, mainly mediated by tumor necrosis factor alpha (TNFα) and interferon gamma (IFN-γ), persistent fever imperils outcomes. A non-resolving febrile state indicates ongoing inflammation, associated with sustained catabolism, malnourishment, muscle mass depletion, and eventually "exhaustion" of the immune system. Causes of such fever are listed in *Table 1*[3].

PRs are a possibly overlooked cause of non-resolving fever in immunocompetent and immunocompromised patients with high-burden tuberculosis disease. Diagnosis requires 1) initial clinical/radiological improvement after initiation of appropriate ATT, 2) "paradoxical" deterioration either at the primary site of disease or at new locations during or after completion of ATT, and 3) absence of other conditions better explaining this deterioration. Diagnosis could be considered approximately two weeks after initiating ATT, although it becomes more likely after two months, and can rarely occur after completion of therapy. PRs are more frequent in patients with extrapulmonary tuberculosis, notably in pleuritis, lymphadenitis, and disseminated disease. The most common intrathoracic manifestation is development or worsening of a pleural effusion. New PR lesions in sites other than the initial presentation only occur in ~25% of all PRs. CNS involvement is of major significance, since tuberculous meningitis-related PRs are associated with high morbidity and mortality, thus requiring aggressive treatment.

As already implied, PRs constitute a spectrum of immunological responses, also including tuberculosis-associated paradoxical inflammatory immune reconstitution syndrome (TB-IRIS)[4,5]. TB-IRIS occurs in the setting of severe immunocompromise, namely in untreated HIV-positive patients initiating antiretroviral treatment. It may also occur in HIV-negative patients after iatrogenic immunosuppression withdrawal, e.g. discontinuation of corticosteroids or TNFα inhibitors, or neutropenia recovery after chemotherapy. Key clinical features are the same as those of PRs in patients without a clear cause of immunosuppression.

Regarding prevention, a recent randomized controlled trial among HIV-positive patients at high risk for TB-IRIS while on ATT showed that concurrent prednisone administration reduced the incidence of TB-IRIS[5], and this strategy has been incorporated in official guidelines as a conditional recommendation for high-risk HIV-positive patients. Treatment approaches differ according to the site and severity of the reaction. If non-severe, a PR may be managed with continuation of ATT and watchful waiting, while non-steroidal anti-inflammatory drugs may be beneficial for symptoms' control. Extending the duration of either the intensive (quadruple therapy) or the maintenance (double therapy) stage of ATT has been attempted, but optimal duration of therapy in these patients remains unclear. High-dose systemic corticosteroids (prednisone, 1mg/kg daily) are warranted in severe cases, occasionally requiring prolonged treatment and slow tapering.

Corticosteroid-refractory PRs are rarely reported, and

Causes	Comments
Disseminated TB or "difficult-to-treat" foci	• Musculoskeletal disease, empyema, cold abscesses (mediastinal, retro-pectoral, retroperitoneal)
Non-adherence, malabsorption, drug resistance	• Lack of compliance may be overcome by providing DOT. • Malabsorption of drugs may be due to TB enteritis, while non-therapeutic drug levels may be due to impaired hepatic metabolism or drug-to-drug interactions. • Multidrug-resistant TB poses a huge threat to global public health.
Adverse drug reactions	• "Common" drug fever • More severe clinical syndromes: Isoniazid-induced lupus (strong ANA positivity is a cardinal finding), drug rash with eosinophilia and systemic symptoms (DRESS syndrome), etc. • Paradoxical reactions
Co-infections	• Superimposed pulmonary infections of bacterial or fungal etiology • Parasitic infections in patients from endemic regions (malaria, amoebic infection, filariasis)
Rare conditions	• Hemophagocytic lymphohistiocytosis, either TB-associated or as a paradoxical reaction[10] • Adrenal insufficiency is mostly associated with night fever due to further hypocortisolemia during the night.

Table 1. *Causes of non-resolving fever in patients with tuberculosis.*

Abbreviations: TB, tuberculosis; DOT, directly observed therapy; ANA, antinuclear antibodies; DRESS, drug reaction with eosinophilia and systemic symptoms.

evidence on how to treat them is scarce. TNFα inhibitors have been used as effective agents[6], with recent data suggest infliximab as a promising adjunct therapy in patients with severe tuberculous meningitis unresponsive to the standard of care[7]. One case of successful treatment with cyclosporine has been described. Interleukin-1 (IL-1) receptor antagonist anakinra, although promising, has been used in very few patients (mostly at a high initial dose of 300 mg daily)[8,9], which further underlines the significance of our patient's response. Recent data suggest inflammasome-mediated IL-1-associated responses as central mediators of innate immunity against *Mycobacterium tuberculosis*. In HIV-positive patients with TB-IRIS, increased plasma IL-1a concentrations (compared to HIV-positive patients without IRIS) could be targeted by blocking IL-1 receptor signaling, while whole-blood transcripts of HIV-positive patients with deteriorating tuberculous meningitis show an upregulation of inflammasome-associated genes via IL-1b activation. Although anakinra is associated with increased susceptibility to infections compared with placebo in rheumatic patients, most infections, even in large referral centers such as our hospital, are non-severe. Opportunistic infections, including mycobacterial infections, are extremely rare. Moreover, anakinra has a short half-life and can be stopped immediately if infectious side-effects occur. Taking its efficacy and safety profile into consideration, anakinra is a useful alternative to treat corticosteroid-refractory PRs to ATT.

CONCLUSION

PRs during tuberculosis treatment can pose significant diagnostic and therapeutic challenges, especially when unresponsive to corticosteroids. This case presents anakinra as a safe and effective alternative in managing corticosteroid-refractory PRs. Biologics may offer a promising adjunct in complex tuberculosis cases requiring individualized treatment approaches to reduce harmful excessive inflammatory responses.

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