Case Report

Severe *Mycobacterium tuberculosis*-related immune reconstitution syndrome in an immunocompetent patient

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Abstract

We present a young immunocompetent male with diagnosed sputum culture-positive tuberculosis on intensive phase with observed daily four-drug antituberculosis therapy. He presented at 1-month of treatment with sequential bilateral pneumothoraces, increase in cavitation and consolidation and respiratory failure. Repeat smears for acid-fast bacilli had downgraded, and cultures were negative. Quantiferon-GOLD (initially negative) was now strongly positive. A diagnosis of possible immune reconstitution syndrome was considered and 0.25 mg/kg/day oral steroids administered.We also discuss an approach to differential diagnosis of a patient worsening on treatment for microbiologically confirmed tuberculosis in this manuscript.

Keywords: Immune reconstitution, pneumothorax, respiratory failure, tuberculosis, Vitamin D

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Introduction

Immune reconstitution reactions are rare in pulmonary tuberculosis, especially in non-immunocompromised patients. We present a 21 year old immunocompetent patient that developed bilateral pneumothoraces and respiratory failure as a result of immune reconstitution syndrome during treatment for pulmonary tuberculosis.

Case Report

A 21-year-old male presented with fever, cough, anorexia and weight loss of 2 months duration. He was a student, did not smoke and did not report alcohol or substance abuse. He did not have any significant medical history and was immunized appropriately. He reported exposure to pulmonary tuberculosis as a caregiver to a sibling 18 months prior to this episode; his sister recovered completely with 6 months of antituberculosis treatment. Tuberculin testing or isoniazid prophylaxis was not offered to the index patient according to current practice in India. He did not raise pets and had stayed alone in a hostel for the last 4 months. Chest radiographs showed bilateral infiltrates and computed tomography [CT, Figure 1] showed findings suggestive of extensive pulmonary tuberculosis. Tuberculin skin testing was negative (6 mm with 5 TU at 72 h). Sputum smears were strongly positive for acid-fast bacilli by Zeihl–Neelsen's stain and supervised daily four-drug antituberculosis treatment (isoniazid 200 mg, rifampicin 450 mg, pyrazinamide 1000 mg, ethambutol 600 mg, pyridoxine 20 mg; weight 40 kg) was initiated and sputum cultures and drug susceptibility for *Mycobacterium tuberculosis* by multiple growth indicator technique (MGIT) was requested. Sputum for GeneXpert for *M. tuberculosis* did not show resistance to rifampicin. Nutrition counseling and four doses of 2-weekly Vitamin D 100,000 I.U were administered as per unit's protocol.[1] He presented with fever, worsening breathlessness, weight loss and chest pain 4 weeks after starting treatment. On examination he was afebrile, normotensive with respiratory rate of 40 breaths/min and pulse rate of 130 beats/min. He was malnourished (body mass inde × 14 kg/m^2, normal

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19–25 kg/m^2). Respiratory examination showed reduced right-sided movements and breath sound intensity with coarse left-sided crackles. Resting SpO_2 was 80%. Chest radiography [Figure 1, left] confirmed the diagnosis of right-sided pneumothorax with increased bilateral infiltrates. He was admitted to the Intensive Care Unit (ICU) with appropriate respiratory isolation; intercostal chest drain was inserted on the right side. There was evidence of air-leak (Cerfolio E)[2] from the right lung with minimal subcutaneous emphysema. Noninvasive positive pressure ventilation (NIPPV) was started; no worsening of air-leak was noted. Repeat sputum smears showed downgrading of smears with scanty acid-fast bacilli by Zeihl–Neelsen's stain. Sputum cultures requested at treatment onset confirmed pan-sensitive *M. tuberculosis*. Repeat CT-chest [Figure 2] showed increase in cavitation, consolidation and ground-glass opacities bilaterally. Further investigations are summarized in Table 1. Fasting blood glucose was 87 mg/dL and human immunodeficiency virus ELISA was negative and there was no CD4 lymphocytopenia. Sputum smears for *Pneumocystis jirovecii* were negative. Urine microscopy was normal and negative for albuminuria. Arterial blood gas analysis showed corrected hypoxemia and respiratory alkalosis (pH 7.42, PO_2 78 mm Hg on FiO_2 0.4, PCO_2 28 mm Hg, HCO_3 22 mEq/L). Quantiferon-TB GOLD in-tube assay was strongly positive. He was continued on four-drug antituberculosis treatment; further doses of Vitamin D were not administered. He developed contralateral pneumothorax on the 2nd day of admission and worsened hypoxemia needing mechanical ventilation. Urgent left intercostal tube drainage was performed and air-leak (Cerfolio I)[2] was noticed on the left side also. Repeat MGIT tuberculosis cultures were reported negative by day 10 of ICU admission.

Discussion

The differential diagnosis of a new or worsening finding in a patient with tuberculosis on treatment includes wrong diagnosis (if diagnosis not microbiologically confirmed), an improper regimen, noncompliance, drug-resistant *M. tuberculosis*, nontuberculosis-mycobacterial disease (HIV-AIDS), super-infection with bacteria or *Pneumocystis jerovicii*, drug hypersensitivity and immune reconstitution. Given the reported rarity of immune reconstitution in HIV-negative pulmonary tuberculosis,[3] we measured cytokines (Bioplex cytokine assay kit; Biorad) and T cell subsets and activation markers by flow cytometry [FACS Cantou II, Beckton Dickinson, Table 1]. The strong interferon-γ responses to RD1 antigens (Quantiferon-Gold) favor the diagnosis of immune reconstitution syndrome (IRIS).

Immune reconstitution is defined as development of new lesions or clinical and/or radiological worsening

Table 1: Laboratory values during ICU Admission of index patient

Parameter	Value	Normal values, range
Hemoglobin g/dL	12.3	12-14
Total leukocyte count cells/μl	14400	4000-11,000
Total platelet counts cells/μl	5.4x10^6	1.5-3.5x10^6
Serum creatinine mg/dL	0.4	0.8
Serum albumin g/dL	2.4	4-5
Serum aspartate aminotransferase IU/mL	53	<50
Serum alkaline phosphatase IU/mL	150	<
Serum bilirubin (total/direct) mg/dL	1.2	0.6-0.8
Total serum calcium mEq/dL	9.0	9-11
Serum phosphate mEq/dL	3.3	3.5-5.5
Urine microscopy	Normal	
Urine albumin	Negative for albuminuria	
Ferritin ng/mL	650	30-400
Anti-nuclear antibody by immunofluorescence negative		
Cytokine panel		
CD3 cells (cells/μL)	72%, 1499	68-80%, 1117-2250/μL
CD4 cells (cells/μL)	60%, 1418	39-57%, 720-1348/μL
CD8 cells (cells/μL)	7.8% 180	17-31%, 318-716/μL
CD19 cells (cells/μL)	1%, 21	8-16%, 151-343/μL
CD16/CD56 cells (cells/μL)	7%, 146	7-21%, 145-453/μL
Myeloid dendritic cells (cells/μL)	0.22%, 17	
Plasmacytoid dendritic cells (cells/μL)	0.02%, 2	
Central memory cells %	25.42	
Naïve cells %	53.8	
Effector memory cells %	12.8	
Terminal effector cells %	7.8	
Interferon gamma pg/mL pg/μL	112	10-42
Monocyte chemotactic protein-1	21.2	
IL-6 pg/mL	9.8	2-29
IL-10 pg/mL	2.0	1-85

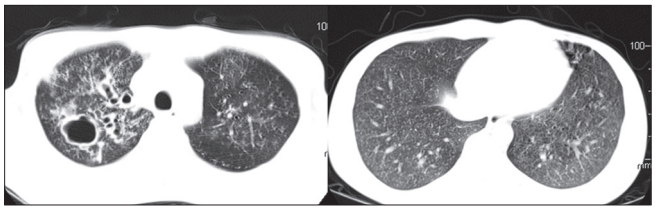

Figure 1: High-resolution computed tomography of the chest at diagnosis showing a large right upper lobe cavity (right) and extensive random nodules in bilateral lower lobes (right)

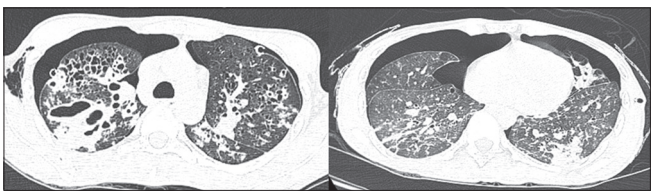

Figure 2: High-resolution computed tomography of the chest after 1-month of treatment showing increase in cavitation and new-onset consolidation and ground glass appearance bilaterally in the upper lobes; bilateral pneumothoraces and intercostal drains are also seen

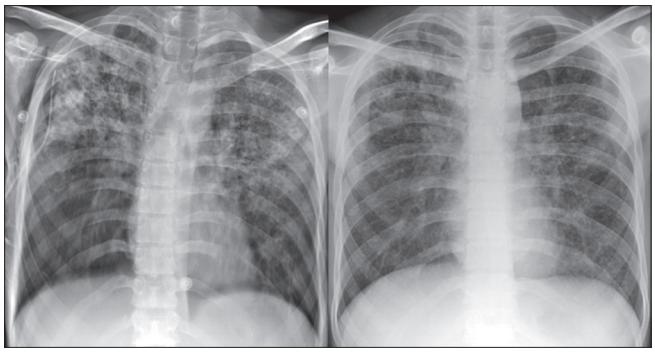

Figure 3: Composite mage of chest radiographs with left, at initial pneumothorax and respiratory failure showing bilateral extensive upper lobe infiltrates and right pneumothorax with intercostals drain. The image on the right at end of treatment shows expanded bilateral lungs with residual fibrosis in the right upper zone

of preexisting (tuberculosis) lesions not attributable to the normal course of disease in a patient (with tuberculosis) initially improving on (antituberculosis) treatment.[4] Immune reconstitution is associated with a wide spectrum of pathogens, most commonly mycobacteria, herpes, and deep fungal infections.[4,5] It has been reported to complicate treatment in 8–36% of HIV-infected patients with tuberculosis.[5] While less is known about immune reconstitution in pulmonary tuberculosis in non-HIV settings, it has been reported in up to 2.4% of patients.[3]

Immune reconstitution in non-HIV setting occurs more commonly in extra-pulmonary tuberculosis and in patients with anemia, malnutrition, hypoalbuminemia and lymphocytopenia at baseline.[3]An association between administration of Vitamin D and immune reconstitution is also reported.[1] Immune reconstitution occurs at varied intervals with a median of 11–46 days after initiation of antituberculosis therapy. Radiological findings suggestive of immune reconstitution in pulmonary tuberculosis includes new or worsening infiltrates and endobronchial lesions, new pleural effusions, new/worsening cavitation and acute respiratory syndrome. Findings suggestive of immune reconstitution in extra-pulmonary tuberculosis include new or enlarging neurological lesions, new or enlarging soft tissue masses and pleural effusions.[6]

Paradoxical reactions have been attributed to immunological causes such as the strengthening of the host's delayed hypersensitivity response, a decrease in suppressor mechanisms as a consequence of increased exposure to mycobacterial antigens secondary to mycobactericidal chemotherapy. There are no diagnostic tests for immune reconstitution; diagnosis is one of exclusion.[6] Recent consensus statements of HIV-related immune reconstitution have stressed that the diagnosis should be made on clinical grounds and that viral load and CD4 assays are not routinely needed.[6]

Treatment of immune reconstitution is controversial; treatment varies from observation, analgesics, nonsteroidal antiinflammatory drugs and steroids depending on the severity of the clinical syndrome. Surgical drainage may be necessary in extra-pulmonary tuberculosis. In scenarios with high-risk for immune reconstitution, a clinical visit must be scheduled and patients counseled appropriately.[3,5]

In the index patient, in view of isolation of pan-sensitive *M. tuberculosis*, good compliance, down-graded smears and negative cultures with therapy and strongly suggestive serological responses, a diagnosis of IRIS was considered and 20 mg prednisolone was administered daily. He improved symptomatically with resolution of fever and constitutional symptoms, weight gain and resolution of right-sided alveolo-pleural fistula. He was extubated to NIPPV support and oxygen tapered. Steroids were tapered over the next 6 weeks. He continued to have left-sided alveolo-pleural fistula requiring thoracotomy and stapling at 4 months of treatment [Figure 3, right]. Continuation phase antitubercular therapy was continued for a total of 8 months. He remains asymptomatic at 1-year of follow-up.

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