

Immune Reconstitution Syndrome Following Initiation of Antiretroviral Therapy in a Patient with HIV Infection and Multidrug-resistant Tuberculosis

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ABSTRACT

Paradoxical exacerbation of the signs and symptoms of tuberculosis may occur not only after antituberculosis therapy, but also soon after the initiation of a potent combination of antiretroviral drugs in human immunodeficiency virus (HIV) seropositive patients with tuberculosis. We report a case of immune reconstitution syndrome in response to antiretroviral therapy in a HIV-positive patient on antituberculosis therapy for multidrug-resistant tuberculosis.

Key words: Immune reconstitution, Multidrug-resistant tuberculosis, Antiretroviral therapy.

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INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) infection has resulted in a dramatic decline in HIV related morbidity and mortality. This decline is mainly due to a drop in the incidence of diseases caused by opportunistic pathogens¹. These changes in natural history of HIV infection seem to occur when HIV replication is brought under control. This in turn allows pathogen specific immune responses to be maintained or restored², leading to an inflammatory response. This exaggerated inflammatory response to an opportunistic pathogen, in HIV infected patients is known as

immune reconstitution syndrome (IRS). This is similar to the paradoxical reaction, described in tuberculosis (TB) patients in the pre-AIDS era, characterised by worsening of the signs and symptoms of tuberculosis, but associated with negative culture and attributed to improved immune responsiveness. In HIV infected patients, IRS has been most commonly described in patients with TB lymphadenitis, *Mycobacterium avium* complex, Cytomegalovirus (CMV)³ or *Cryptococcus neoformans*⁴ infections.

We report a case of IRS after initiation of antiretroviral therapy (ART) in a patient receiving antituberculosis therapy (ATT), for multidrug-resistant tuberculosis (MDR-TB).

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CASE REPORT

A 28-year-old lady presented to the HIV clinic of Tuberculosis Research Centre, in September 2003, with complaints of dry cough, intermittent headache, and weight loss of greater than six kilograms over a nine-month period. Her husband had died of AIDS and TB, seven years ago; treatment details of which were not available. She was known to be HIV-positive but in apparently good health till she developed these complaints. There was no previous history of treatment for tuberculosis.

She weighed 65.0 kg and was in good general condition. Bacille Calmette-Guerin (BCG) scar was absent. Respiratory system examination revealed scattered crepitations in the right mammary and infra-axillary areas. Her haematology and blood biochemistry results were within normal limits. She was asked to provide three-overnight/early morning specimen of sputum for bacteriological examination. Sputum smears were negative for acid-fast bacilli (AFB). Chest radiograph (Figure 1) showed prominent bronchovascular markings. Mantoux test with 1 TU was 2.5 mm at 48 hours. Her plasma HIV

viral load was 72,500 copies/ml, (Roche Cobas Amplicor automated viral load monitor). CD4+ T cell percentage was measured by flow cytometry (Coulter Epics Altra) using a three-colour panel of monoclonal antibodies (CD3/CD4/CD8). CD4+ T cell count was calculated by multiplying the CD4% with absolute lymphocyte count. Her CD4+ T-cell count was 90 cells/mm³. Contrast enhanced computed tomographic scan (CECT-scan) of the chest (Figure 2) showed evidence of focal areas of fibrosis, reticulonodular lesions in the posterior basal segments of both lungs, more on the left side. There was also evidence of fibrous strands in the right middle lobe (Figure 2). In view of the clinical and radiological abnormality, she was started on antituberculosis therapy (ATT) with Revised National Tuberculosis Control Programme (RNTCP) category I treatment using (thrice weekly regimen of ethambutol (1200 mg), isoniazid (600 mg), rifampicin (600 mg) and pyrazinamide (1500 mg) and 10 mg of pyridoxine along with one tablet of cotrimoxazole DS (double strength) daily. Pre-treatment sputum cultures were negative for *Mycobacterium tuberculosis*.

Soon after starting ATT, patient complained of severe itching all over her body, especially on the days she consumed ATT. By drug

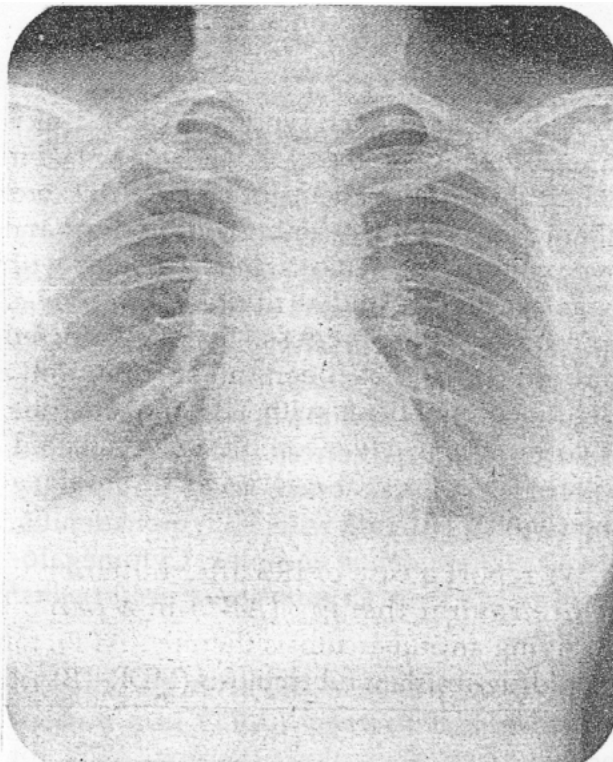


Figure 1. Chest radiograph (PA view) showing prominent bronchovascular markings.

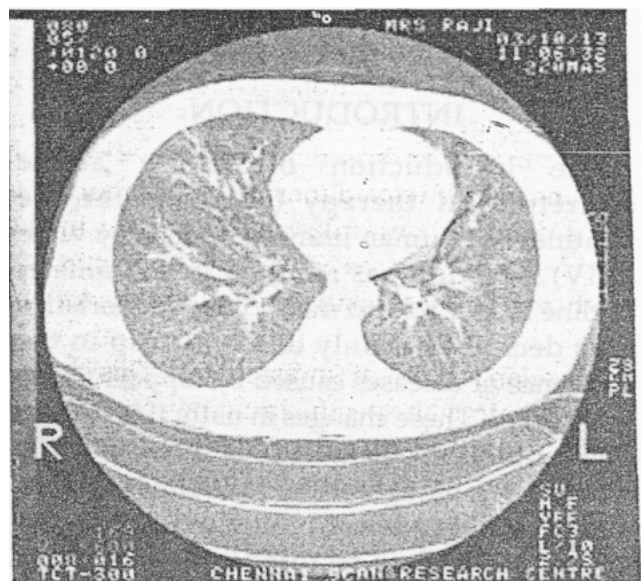


Figure 2. CT scan of the chest showing focal areas of fibrosis, reticulonodular lesions in posterior basal segments of both lungs.

exclusion strategy, the offending agent was identified as pyrazinamide and it was withdrawn as she did not respond to symptomatic management. Patient began to improve symptomatically. She was supplied drugs once a week as she was working and direct observation of treatment was not done. In November 2003, her sputum smears became positive and culture grew *M. tuberculosis*. Sensitivity tests were set up then.

By January 2004, patient developed productive cough, evening rise of temperature and weight loss of two kilograms. Her chest radiograph (Figure 3) showed signs of deterioration with a parenchymal opacity along the right horizontal fissure. In the next few weeks, sensitivity reports became available, that showed a resistance pattern to all the four first line antituberculosis drugs, namely ethambutol, isoniazid, rifampicin and streptomycin. Pyrazinamide sensitivity was not done. She was diagnosed to have multidrug-resistant tuberculosis (MDR-TB) and was started on kanamycin (1.0 gm), thrice weekly along with

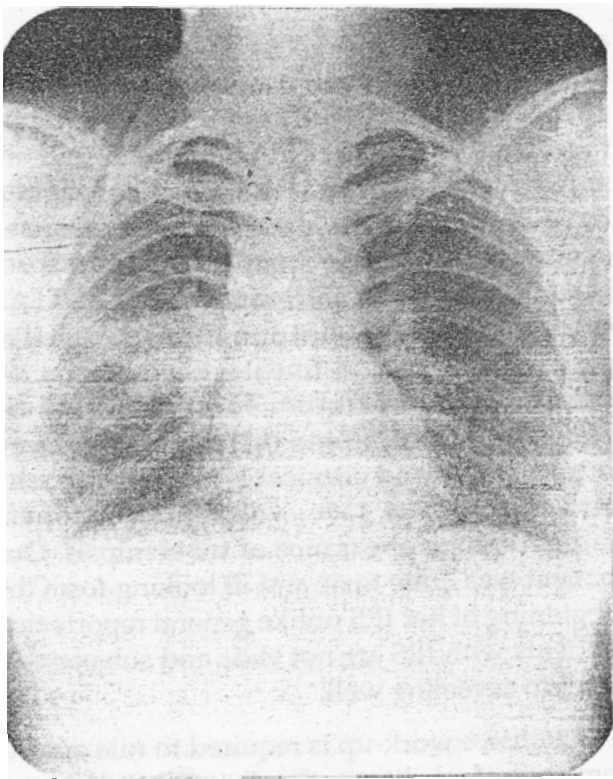


Figure 3. Chest radiograph (PA view) showing signs of linear parenchymal opacity along the right horizontal fissure.

daily ofloxacin (600 mg), ethambutol (800 mg), cycloserine (500 mg) and ethionamide (500 mg).

By late February 2004, her CD4+ cell counts dropped to 65 cells/mm³ and her body weight was 63.0 kilograms. In view of continuous vomiting induced by ethionamide, this drug had to be withdrawn and she continued with the rest of the drugs without any complaints. At the same time, she was also started on triple drug regimen of antiretroviral therapy (ART) with stavudine (40 mg), lamivudine (150 mg) and nevirapine (200 mg) all given twice daily, after the initial dose escalation for nevirapine. Patient started showing signs of clinical improvement.

Three weeks after the initiation of ART, the patient developed continuous high-grade fever, breathlessness and productive cough. On examination, she was dehydrated, toxic, and on auscultation of chest, coarse crepitations were heard all over the right lung. She was hospitalised in a private institution and managed symptomatically with intravenous fluids, broad-spectrum antibiotics and antipyretics. Patient continued to have high-grade fever. Again a complete blood count, liver function and renal function tests, chest radiography, sputum culture for fungal and bacterial pathogens, blood Widal and urine culture were done. Peripheral smears for malarial and filarial parasites were negative. Chest radiograph showed right upper zone and middle zone consolidation, worse than the previous chest radiograph, that was obtained a month ago (Figure 4). Out of the six sputum specimens collected, only one smear was positive for AFB. Her haemoglobin was 9.2 gm% with a CD4+ cell count of 114 cells/mm³.

Rapid tests for hepatitis B and C, tests for antibodies to CMV and toxoplasma were negative. Her blood culture and urine culture did not show any growth. Hence, a diagnosis of IRS was considered and paracetamol was administered. Patient continued to have fever and cough. She was also losing weight and by the end of March 2004 she was only 52.0 kilograms. She became very depressed and withdrawn.

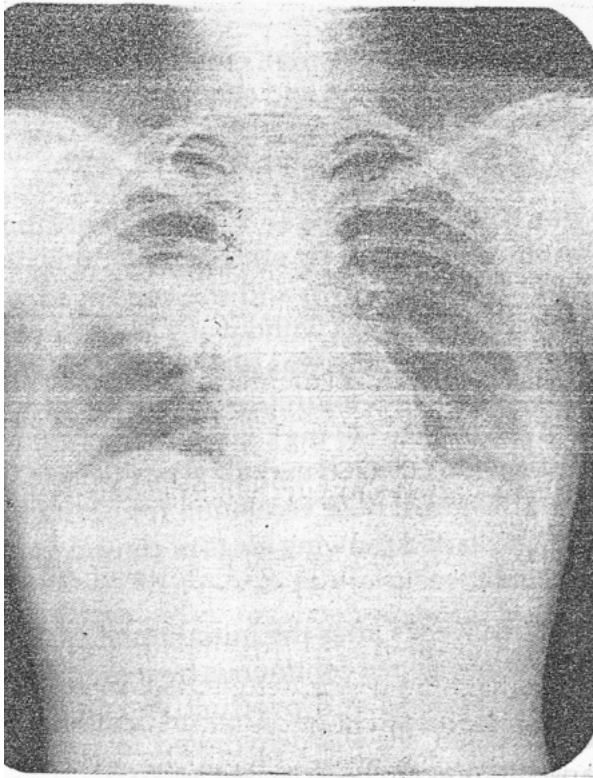


Figure 4. Chest radiograph (PA view) showing increasing consolidation of right upper and middle lobes.

In view of her worsening clinical condition and with the working diagnosis of IRS, she was started on daily oral prednisolone (1 mg/kg bodyweight) and was monitored closely. Within a week of starting oral corticosteroids, patient started showing signs of improvement. Her fever subsided; her oral intake increased and she became more cheerful. After 10 days at this dosage, oral prednisolone was tapered at the rate of 5 mg per week over a period of two months. Meanwhile she continued to receive ART and drugs for the treatment of MDR-TB. Chest radiograph repeated after one month, showed regression of lesions in right upper and middle lobes (Figure 5). There was no evidence of any new pulmonary lesion. She began gaining weight (59.0 kg) as well as self-confidence. Twelve weeks after starting ART, her viral load was below 400 copies/ml and her CD4+ count rose to 204 cells/mm³.

DISCUSSION

We have described a patient with MDR-TB

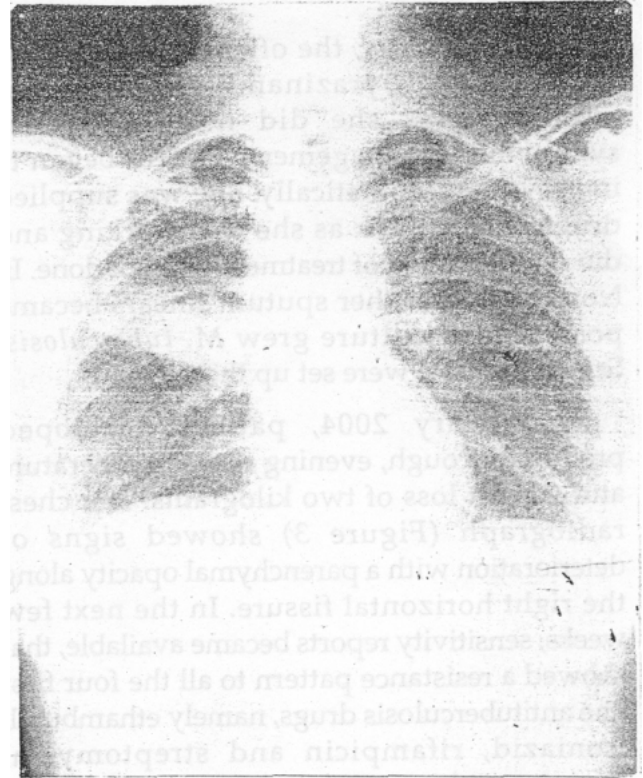


Figure 5. Chest radiograph (PA view) showing signs of regressing lesion in the right upper and middle lobe. There is no evidence of any fresh pulmonary lesions.

and immunosuppression due to HIV, who developed exacerbation of her TB symptoms along with deterioration of her chest radiograph, soon after the initiation of potent antiretroviral therapy. Narita and colleagues⁵ have reported that “paradoxical response” occurs in 36% of patients with HIV-TB co-infection after the initiation of HAART. An event rate of 30-40% has also been estimated in patients who start treatment with low (ie., <100 cells/ μ l) CD4+ counts⁶. The most common clinical manifestations include hectic fever, intrathoracic and cervical lymphadenopathy and like in our case, worsening of chest radiographic appearance of tuberculosis. Our patient was quite toxic and ill looking from the beginning of her IRS unlike general reports that patients with IRS are not toxic and subjectively refer to as feeling well.

Extensive work-up is required to rule out the presence of condition other than TB as the cause of fever, before making a diagnosis of IRS in these patients. These include looking for the

presence of other opportunistic pathogens, like cytomegalovirus, toxoplasma salmonella, non-tuberculous mycobacteria and other organisms. Our patient was repeatedly tested for AFB in sputum during her febrile episodes and they were negative at all occasions except once. In a case of IRS with worsening respiratory symptoms, evidence of increasing *M. tuberculosis* replication is usually lacking. Chest radiographic appearances can vary from new pulmonary infiltrates, pleural effusion, miliary infiltrates or worsening of the original tuberculous lesions⁵.

Delayed type hypersensitivity response to tuberculin usually appears where it was absent before starting HAART. This also indicates HAART's restoration of anti *M. tuberculosis* cell mediated immune response⁷. Paradoxical reactions have been attributed to immunologic causes such as the strengthening of the host's delayed hypersensitivity response or a decrease in suppressor mechanisms⁸. Like in our patient, the TB signs and symptoms may worsen after initiation of ART.

Our patient had a very low CD4+ cell count at the initiation of ATT and ART. Generally, paradoxical responses occur in patients with a CD4+ T-cell count of less than 100 cells/ μ l before the initiation of HAART, which increases significantly after HAART is underway⁹. One study¹⁰ showed that immune reconstitution events start at a median time from the start of antiretroviral therapy of 22.5 days.

Inflammation associated with restoration of anti *M. tuberculosis* cell mediated immunity after commencing HAART is usually controlled by the use of anti-inflammatory therapy, including corticosteroids. Our patient responded to oral prednisolone treatment. Her antiretroviral therapy and antituberculosis treatment were continued uninterrupted throughout her period of immune restoration. The general treatment strategy of IRS includes continuation of ARV therapy, addition of antimicrobial therapy to suppress the replication of related pathogens and anti-inflammatory therapy. Rarely, if this approach fails, ARV therapy may have to be discontinued at least temporarily.

The main reason for reporting this case is the diagnostic dilemma faced when patients on ARV and TB treatment develop clinical deterioration. What are the likely causes of these abnormalities, when no demonstrable pathogens are identified? Should corticosteroids be started for patients on TB treatment? Should the ARV be withdrawn? The timing, clinical manifestations and radiographic changes in the present case suggested that all the clinical events were due to the immunologic changes associated with successful ART. This case demonstrates that AIDS associated TB including MDR-TB can worsen during the initial weeks of successful chemotherapy and can also flare up, sometimes at new sites. Treatment failure, drug fever and the development of non-TB HIV-related conditions were considered unlikely here since an extensive infectious work-up was negative and the clinical symptoms and lesions subsided despite continuation of the same TB treatment. Use of short-term corticosteroid treatment (46 weeks) that suppresses the enhanced immune response, while maintaining patient on appropriate ATT and antiretroviral therapy proved to be helpful, even in a case of MDR-TB.

In summary, a paradoxical exacerbation of signs and symptoms of tuberculosis may occur not only after ATT, but more commonly, soon after the initiation of potent combination of ART in HIV infected TB patients. A thorough investigation is necessary to exclude other aetiological causes before a diagnosis of immune reconstitution can be made. It is important that treating clinicians be aware of this phenomenon and realise that this simply represents an enhanced immune response to *M. tuberculosis* antigens following potent combination antiretroviral therapy and not treatment failure, drug reaction or other non-TB HIV related illnesses.

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