**Case Report**

**ACUTE RESPIRATORY DISTRESS SYNDROME AS A PARADOXICAL RESPONSE TO ANTI-TUBERCULOSIS AND ANTI-RETROVIRAL THERAPY**

H.S. Subhash¹, S. Supriya², B. Prakash³ and K. Thomas⁴

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**Summary:** Paradoxical response or immune reconstitution inflammatory syndrome (IRIS) during the course of anti-tuberculous therapy is being increasingly recognised among patients with and without HIV co-infection. A 40-year-old HIV infected male on anti-retroviral therapy (ART) presented with persistent fever and weight loss. He was diagnosed to have miliary tuberculosis and HIV co-infection. Following initiation of anti-tuberculous chemotherapy, the clinical course was characterised by development of acute respiratory failure (ARDS) as a paradoxical response/IRIS to treatment. This uncommon manifestation of paradoxical response (ARDS) in HIV and tuberculous co-infection following initiation of ART and anti-TB treatment is very scarcely reported in the past. With the increasing incidence of HIV/AIDS and TB co-infection along with liberal access to ART in the developing world, it is likely that paradoxical reactions will be encountered more frequently. *Indian J Tuberc 2006; 53:157-160*

**Key words:** Tuberculosis, AIDS, ARDS, Paradoxical response, IRIS, ART, HAART.

**INTRODUCTION**

Paradoxical worsening of tuberculosis symptoms in response to initiation of anti-tuberculous therapy is well recognised for many years in non-HIV infected individuals.¹⁻² The most common of such paradoxical response is worsening of fever and development of new or increase in size of already existing lymph nodes in both HIV infected and non-infected individuals.³⁻⁴ Over the past few years, paradoxical response, also called as immune reconstitution syndrome (IRS) or immune reconstitution inflammatory syndrome (IRIS) is more frequently noted in patients co-infected with HIV and tuberculosis especially after the introduction of highly active anti-retroviral therapy (HAART).⁵⁻¹⁰ Acute respiratory distress syndrome (ARDS) manifesting as a paradoxical response to initiation of anti-TB medication is very rarely noted in patients with pulmonary tuberculosis.² However, in miliary tuberculosis, it is well known to occur among non-HIV infected patients and there are numerous publications on this aspect in the literature.¹¹⁻¹³ Acute respiratory distress syndrome as a manifestation of IRIS in HIV infected tuberculosis patients is not well described and there are only occasional reports of this condition in the literature.¹⁴⁻¹⁵ Here we report a paradoxical response/IRIS presenting as ARDS following initiation of anti-TB and HAART treatment in an HIV infected TB patient. We have also made an attempt to briefly review IRIS in HIV and tuberculosis co-infection in this article.

**CASE REPORT**

A 40-year old man was diagnosed to have HIV infection in a community hospital when he presented with complaints of low-grade intermittent fever, mild productive cough and significant weight loss over 4 months. He was referred to our centre six weeks after initiation of treatment with anti-retroviral (ART) drugs consisting of Zidovudine 600 mg a day, Lamivudine 300 mg a day and Nevirapine 400 mg daily for evaluation of persisting fever and weight loss.

Physical examination revealed a thinly built individual with significant pallor but otherwise...
unremarkable systemic examination. Investigations revealed hemoglobin of 7.8 gm/dl and total leukocyte count of 2,300 cells/cu mm. Liver function showed total bilirubin 1.2 mg %, direct bilirubin 0.7 mg %, total protein 8.5 gm %, albumin 2.4 g %, SGOT 142 U/L, SGPT 54 U/L, alkaline phosphatase 862 U/L. Electrolytes and serum creatinine were normal. HIV antibody was positive by ELISA test. HbsAg and VDRL were negative. Blood cultures and smear for malarial parasites were negative. Three consecutive morning samples of sputum were negative for AFB. Chest radiograph (Fig.1) showed diffuse miliary nodules bilaterally suggestive of miliary tuberculosis. Bone marrow biopsy showed evidence of granulomatous infiltration consistent with tuberculosis. Subsequently, bone marrow culture grew two colonies of morphologically typical Mycobacterium tuberculosis.

A diagnosis of disseminated tuberculosis was considered and the patient was initiated on standard anti-TB regimen consisting of Isoniazid 300mg daily, Rifampicin 450mg daily, Pyrazinamide 1.5g daily and Ethambutol 800mg daily. Co-trimoxazole was given for Pneumocystis carinii pneumonia prophylaxis. While he was in the hospital awaiting further evaluation of CD4 cell count and HIV viral RNA load, he developed sudden onset of dyspnoea, tachypnea, cyanosis and bilateral crepitations on the third day after initiation of antituberculous treatment. An arterial blood gas showed severe hypoxemia with a PaO2 of 35 mm Hg and PaCO2 of 19 mm Hg on breathing room air. Chest radiograph (Fig. 2) showed extensive bilateral fluffy alveolar shadows suggestive of acute respiratory distress syndrome (ARDS). Despite supplementary O2 therapy and resuscitation measures he progressively worsened and died within a few hours.

DISCUSSION

Paradoxical response to tuberculosis treatment is well known to occur in both HIV and non-HIV infected individuals4. Various manifestations of paradoxical response are described, such as worsening fever, development of new or increase in size of already existing lymph nodes and enlargement of cerebral tuberculomas, etc1,3,6. Paradoxical response during the course of treatment is attributed to an immunological consequence of drug therapy precipitated by highly immunogenic cell-wall products/antigens of the mycobacterium being released during the course of bactericidal chemotherapy2.

Paradoxical worsening of pulmonary lesions, leading to respiratory failure, although rare, are more commonly noted in miliary tuberculosis
than in non-miliary pulmonary tuberculosis among patients without HIV infection\textsuperscript{11-13}. They are associated with high fatality when it occurs in miliary TB\textsuperscript{11}. Respiratory failure in miliary tuberculosis is postulated to be secondary to extensive pulmonary involvement and also due to a hypersensitivity reaction following initiation of bactericidal anti-TB chemotherapy. In turn, this leads to damage of the alveolar-capillary membrane leading to increased permeability resulting in respiratory failure (ARDS)\textsuperscript{2}.

Paradoxical response or immune reconstitution inflammatory syndrome (IRIS) is more frequently recognised in patients co-infected with tuberculosis and HIV, especially among those who are initiated on combination ART\textsuperscript{5,7}. This is thought to be related to host immune restoration in the presence of mycobacterial antigen during the course of ART therapy\textsuperscript{5,7}. This manifests usually four to ten weeks after initiation of ART, more frequently noted with extrapulmonary and disseminated TB\textsuperscript{14}, generally self-limiting, last for about 10 to 14 days\textsuperscript{5,10}. It is also noted that patients who develop tuberculosis 1-4 months after starting ART are more prone to develop significant IRIS compared to those who develop TB later\textsuperscript{17}. Acute respiratory distress syndrome manifesting as IRIS in HIV and tuberculosis co-infection is extremely rare and there are only a few reports of this condition in the literature\textsuperscript{14,15}. Earlier published reports suggest that IRIS coincides with starting of ART among HIV infected TB patients who are already on anti-TB therapy (anti TB followed by anti-retroviral therapy)\textsuperscript{4}. The patient presented here was on anti-retroviral therapy for a period of one and half months prior to our initiating him on anti-TB drugs. He developed the IRIS within a span of three days after the initiation of anti-TB therapy (anti retroviral followed by anti-TB). It is reasonable to assume that in this patient the paradoxical response was related to exposure to mycobacterial antigens following bactericidal TB chemotherapy in the presence of heightened immunity. The explosive nature of the response in this patient was probably related to the immune reconstitution related to the prior ART.

Though the patient presented here had definitive evidence of disseminated tuberculosis, we were unable to exclude other concomitant infections because of the rapid worsening of the acute illness, such as Pneumocystis carinii pneumonia and other uncommon infections, which can present with respiratory failure in the background of HIV infection even though he was on co-trimoxazole prophylaxis.

This case is presented to highlight that IRIS can manifest as ARDS in HIV infected individuals who are initiated on anti-TB treatment and ART. With the increasing incidence of HIV/AIDS and TB co-infection in developing world along with liberal access to ART for these individuals, it is likely that IRIS will be encountered more frequently in atypical forms. However, other concomitant conditions need to be excluded. Failure to recognise ARDS secondary to IRIS may lead to provisional therapy for other more common pulmonary conditions and other opportunistic infections\textsuperscript{14}. Moreover, in anecdotal case reports, mechanical ventilation and corticosteroids are shown to be helpful\textsuperscript{14}. However, the usefulness of these interventions in HIV infected individuals presenting with this condition need to be studied further.

REFERENCES


