Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Case Report

Immune reconstitution inflammatory syndrome

Brig M.S. Barthwal^a, Maj Yadvir Garg^{b,*}, Col D. Bhattacharya^c,
Col C.D.S. Katoch^d, Brig A.K. Rajput^e, Lt Col V. Marwah^f

^a Commandant, Military Hospital Mhow, C/o 56 APO, India^b Graded Specialist (Respiratory Medicine), Army Hospital (R&R), New Delhi 10, India^c Senior Advisor (Medicine & Respiratory Medicine), Military Hospital (Cardiothoracic Centre), Pune 411040, India^d Senior Advisor (Medicine & Respiratory Medicine), Military Hospital Namkum, C/o 56 APO, India^e Consultant (Medicine & Respiratory Medicine), Army Hospital (R&R), New Delhi 10, India^f Classified Specialist (Respiratory Medicine), Army Hospital (R&R), New Delhi 10, India

ARTICLE INFO

Article history:

Received 7 March 2014

Accepted 7 July 2014

Available online 8 October 2014

Keywords:

Immune reconstitution syndrome

Tuberculosis

HIV

Cytomegalovirus

HAART

Corticosteroid

documented with other pathogens and even with non infectious disorders as well. We describe here a patient with acquired immunodeficiency syndrome (AIDS) who developed IRIS in more than usual period of 2–4 weeks,² after initiation of highly active anti-retroviral treatment (HAART). Moreover this patient suffered TB-IRIS well after the defined time frame of 3 months after the initiation of ART as described in case definition for Paradoxical TB-IRIS.³

Case report

A 36-year-old male presented with a history of fever, cough and streaky hemoptysis of three weeks duration. On evaluation hematological and biochemical parameters were within normal limits. Chest radiograph showed alveolar opacities over left middle zone with cavitation. Sputum examination revealed acid fast bacilli (AFB). MTB culture was positive and sensitive to first line drugs. Mantoux test was 4 mm in diameter. The patient tested positive for HIV-1 and CD4+ T-cell count was 137/μL. He was started on four-drug daily supervised antituberculosis treatment (ATT) with isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1500 mg and ethambutol 800 mg. After around 2 weeks of ATT, he improved clinically with subsidence of fever, cough and hemoptysis. Anti-retroviral treatment (ART) comprising of zidovudine 300 mg twice daily; lamivudine 150 mg twice daily

Introduction

Immune reconstitution inflammatory syndrome (IRIS) is defined as occurrence or worsening of clinical and/or laboratory parameters despite a favorable outcome in human immunodeficiency virus (HIV) surrogate markers.¹ It has been described in 5%–10% of HIV seropositive patients with CD4+ T-cell count less than 200/μL and occurs most commonly with mycobacterial and CMV infections, though it has also been

* Corresponding author. Tel.: +91 (0)11 23338152, +91 8130831116.

E-mail address: docyadvirgarg@gmail.com (Y. Garg).

<http://dx.doi.org/10.1016/j.mjafi.2014.07.003>

0377-1237/© 2014, Armed Forces Medical Services (AFMS). All rights reserved.

and efavirenz 600 mg once daily at night was initiated after two weeks of ATT.

After about 18 weeks of ATT and 16 weeks of ART, he started having watery diarrhea, high grade fever and reappearance of cough with mucoid expectoration. On examination, he was febrile, had tachycardia and tachypnea. Investigations showed normal blood counts, sputum smear positive for acid fast bacilli and blood and stool culture was sterile. Chest radiograph showed alveolar opacities with cavitation (progression of lesions as compared to previous radiograph). Contrast enhanced computed tomography (CECT) scan chest showed areas of consolidation in lingular region. The patient was empirically treated with broad spectrum parenteral antibiotics for 2 weeks with no response.

In view of persistent sputum positivity, progression of lesions on chest radiograph, possibility of MDR TB was considered and MTB culture was repeated. Pending culture reports he was started on second line ATT (Lfx, Km, Eto). However, despite 4 wks of 2nd line ATT, he continued to be symptomatic with cough with expectoration and low grade fever and in addition developed breathlessness. Systemic examination revealed cervical lymphadenopathy, cold abscess over anterior chest wall (Fig. 1) and absent breath sounds left infraxillary and infrascapular area. Chest radiograph revealed findings suggestive of left sided pleural effusion. Pleural fluid aspiration revealed lymphocytic exudate with adenosine diaminase (ADA) level of 40 IU/L. Repeat CD4+ T-cell count was 180/ μ L. Fine needle aspiration cytology was suggestive of tubercular lymphadenitis with Z–N staining positive for AFB. His repeat sputum MTB culture showed no growth. As there was progression of tubercular disease in HIV positive patient despite having drug susceptible tuberculosis with good compliance to ATT, possibility of IRIS was considered and he was started on oral prednisolone (1 mg/kg/day). After one week of oral steroids, his symptoms started subsiding with gradual reduction in the size of lymph nodes and chest wall abscess. His second line ATT was stopped and he was continued on first line ATT. He became asymptomatic with complete regression of lymph nodes, chest wall abscess (Fig. 2), pleural effusion and significant regression of pulmonary lesions after four weeks of steroids. Steroids were tapered off after four weeks and ATT and ART were continued.

Fig. 1 – Lymphadenopathy in left suprascapular region and left chest wall abscess.

Fig. 2 – Resolution of lymphadenopathy and chest wall.

Discussion

In the case of TB, two forms of IRIS are recognized.³ Paradoxical TB-IRIS occurs in patients diagnosed with TB and established on TB treatment before ART, who then manifest with recurrent or new TB symptoms and clinical manifestations after ART initiation. Unmasking TB-IRIS occurs in patients who are not on TB treatment when they start ART, and who then have an unusual inflammatory presentation of TB in the first 3 months of ART.

As a form of deterioration during TB therapy, paradoxical TB-IRIS often seems more severe, and frequently involves multiple organ systems. Paradoxical reactions are far more frequent (36%) after ART initiation than in patients not infected with HIV-1 (2%) and patients infected with HIV-1 and not on ART (7%).⁴ As per the NACO guidelines in case of HIV and TB coinfecting patients start ATT first, thereafter initiate ART as early as possible between 2 weeks and 2 months when TB treatment is tolerated in order to reduce the incidence of IRIS and minimize side effects of treatment.⁵ In our case ART was initiated after 2 weeks of ATT when he was tolerating ATT and showing clinical improvement with it. The median interval from ART initiation to onset of paradoxical TB-IRIS is typically 2–4 weeks.² However present case had unusually long interval of 16 weeks.

Pathogenesis of IRIS is generally thought to be the restoration of the immune responses to antigens (viable or not) producing exuberant inflammatory reactions. Given the fact that shortly after the initiation of HAART there is a rapid recirculation of memory cells these memory cells may play a role in the development of IRIS.⁶

The most frequent clinical features are recurrent symptoms, fever, enlarging inflammatory lymph nodes, and new or enlarging serous effusions. In addition, worsening of radiographic pulmonary infiltrate is seen in upto 45% of TB patients starting ART, and patterns observed include consolidation, cavitation, miliary infiltrates, and cystic changes.⁷ Subcutaneous and deep tissue abscesses may form. Our case had most of these features.

Paradoxical TB-IRIS is diagnosed on the basis of a characteristic clinical presentation, temporal relationship to the initiation of ART, and exclusion of alternative explanations for clinical deterioration.³ It is important to factor and investigate for other opportunistic infections and malignancies, TB

treatment failure (due to nonadherence, TB drug resistance, or malabsorption of TB drugs), or drug reaction.

There are no standard guidelines for the treatment of IRIS. Most cases resolve without additional treatment. Mild cases require reassurance and symptomatic treatment. In cases with more significant symptoms, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have been used.⁸ Corticosteroid therapy may exacerbate other untreated infection or drug resistant TB, so should only be considered for TB-IRIS when alternative diagnoses have been excluded. The present case was started on oral steroids after systematically ruling out other infections and drug resistant tuberculosis. Corticosteroids at a dose of 20–40 mg/day for 2–4 weeks may be helpful in the presence of persistent fever, abscesses, dyspnea or meningitis.

In the case of life-threatening forms of TB-IRIS, such as tuberculous meningitis with increased intracranial pressure, stopping ART temporarily could be considered.

REFERENCES

1. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. 2004;18:1615–1627.
2. Breen RAM, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004;59:704–707.
3. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis associated immune reconstitution inflammatory syndrome: case definitions for use in resource limited settings. *Lancet Infect Dis*. 2008;8(8):516–523.
4. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998 Jul;158(1):157–161.
5. Office Memorandum on Revised Guidelines on Initiation of ART in Adults and Adolescents. New Delhi: Dept of AIDS control Govt of India NACO Guidelines; 2011.
6. Pakker NG, Notermans DW, De Boer RJ, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. *Nat Med*. 1998;4:208–214.
7. Fishman JE, Saraf-Lavi E, Narita M, Hollender ES, Ramsinghani R, Ashkin D. Pulmonary tuberculosis in AIDS patients: transient chest radiographic worsening after initiation of antiretroviral therapy. *AJR Am J Roentgenol*. 2000 Jan;174(1):43–49.
8. Swaminathan S, Nagendran G. HIV and tuberculosis in India. *J Biosci*. 2008 Nov;33(4):527–537.