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Role of tuberculin testing in predicting immune reconstitution response after antiretroviral therapy in patients with HIV-TB co infection

KEYWORDS: Immune reconstitution, HAART, Tuberculin testing

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ABSTRACT *Background – Suppression of HIV replication by HAART often restores protective pathogen specific immune responses, but in some patients the restored immune response causes various pathological manifestations termed as immune reconstitution.*

Objective- To review clinical profile of HIV patients exhibiting immune reconstitution after starting HAART and to assess whether restoration of tuberculin skin testing can alert us from such response.

Material and methods- This prospective study over 18 months, included 40 HIV positive patients with tuberculosis receiving antituberculous treatment and who were subsequently started on HAART. Tuberculin testing was performed on all the patients before ART. They were followed up monthly. Patients who showed symptomatic worsening, deterioration of laboratory/radiological investigations but improving CD4 count were kept under observation. After extensive work up to rule out causes such as treatment failure, other HIV related opportunistic infections etc, patients were defined to have immune reconstitution. Tuberculin testing was repeated in such patients at the time of worsening and in other patients monthly for 6 months.

Observation and results- 5 out of 40 patients showed immune reconstitution as per the definition. Clinical profile, base line CD4 count, radiological and laboratory parameters of such patients were studied. Tuberculin testing turned to positive in all 5 patients. It remained negative in all other patients. Mean baseline CD4 count of patients without immune reconstitution was 184/cmm, and with immune reconstitution was 58.6/cmm. This difference was clinically significant. Mean time interval to develop immune reconstitution was 31 days.

Conclusion and summary- immune reconstitution was seen on 5 put of 40 patients (12.5%). These patients had low mean CD4 count at the baseline. All patients (100%) exhibited restoration of tuberculin testing. This restoration can be utilized as a predictor of immune reconstitution, an atypical but clinically important phenomenon.

Introduction

The administration of highly active antiretroviral therapy (HAART) has produced a significant decrease in opportunistic infection but also has changed natural history and the usual presentation of some of these infections. Initiation of ART is sometimes followed by paradoxical worsening of clinical or laboratory parameters despite favorable response i.e. increase in CD4 count (1). This phenomenon is termed as immune reconstitution. It occurs due to marked improvement of immune function both qualitative and quantitative (2). Interestingly, many patients who were anergic to Tuberculin skin testing develop strongly reacting test after ART.

Immune reconstitution although transient and usually self limited, sometimes do lead to life threatening consequences. Examples include an enlarging tuberculoma raising intracranial tension, enlarging lymph nodes causing airway compression etc. It also creates anxiety in both, the patient and treating physician, noncompliance to treatment and pose diagnostic dilemma. Hence an attempt was made to study clinical profile of patients who develop such immune reconstitution after ART. Special consideration was given to conversion of anergic tuberculin testing in patients before starting ART to a positive response.

Details of study

Aims and objectives-

1. To study clinical profile of patients of HIV –TB co infection who develop immune reconstitution after initiation of antiretroviral therapy.
2. To find out association of tuberculin test conversion from negative to positive with immune reconstitution.

Material and methods

This was a prospective study conducted in a general hospital over 18 months. It included 40 patients of HIV TB co infection after written informed consent. HIV infection was diagnosed by ELISA test. Tuberculosis was diagnosed by clinical findings with consistent radiological and/or bacteriological evidence.

Patients were further classified as having pulmonary or extra pulmonary tuberculosis. Patients underwent following work up at the start of study-

1. Complete blood count
2. Baseline CD4 count
3. Chest X ray
4. USG abdomen
5. Bacteriological study of sputum, pleural fluid, ascetic fluid, cerebrospinal fluid wherever necessary.
6. Tuberculin skin testing.

Negative TT was defined as induration of less than 5mm at the end of 24 hours.

Positive TT was defined as induration more than 5 mm.

7. Relevant investigations to rule out opportunistic infections apart from TB.
8. Metabolic Lab which included liver function tests, lipid

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profile etc.
Patients diagnosed as HIV TB confection were started first on antituberculous treatment according to DOTS category. After 2 months, Patients according to CDC guidelines were put on Efavirenz based three drug regimen. Tuberculin testing of each patient was performed at the start. Patients were followed up prospectively every monthly and whenever an immune reconstitution was noted.

Immune reconstitution was defined as follows-

1. New persistent fever (temperature >101.5F) which developed after the initiation of
ART and which lasted for more than a week without an identifiable source despite an

extensive fever work up (eg. multiple blood culture, urine and sputum examination)

2. Marked worsening or emergence of intrathoracic lymphadenopathy, pulmonary
infiltrates, pleural effusion as evidenced on follow up chest X ray.

3. Worsening or emergence of cervical lymphadenopathy on serial physical examination.
3. Fresh findings on review USG abdomen.

Tuberculin skin testing was repeated at monthly interval of initiation of ART and at the time of development of immune reconstitution. At the end of six months clinical profile of patients with immune reconstitution was studied with along with site of tuberculosis, baseline CD4 count and time interval from initiation. CD4 count repeated at time of immune reconstitution was found to be increased above the baseline value. This ruled out possibility of treatment failure. Focus was maintained to assess correlation of conversion of TT with development of immune reconstitution and in such case whether TT can be a valuable tool in predicting immune restoration.

Observation and results
Out of 40 patients 26 were males and 14 were males. Mean age was 34 years. 15 patients had pulmonary tuberculosis and 17 patients had extrapulmonary tuberculosis. 8 Patients had disseminated tuberculosis.

Table 1 showing distribution of extra pulmonary sites
All 40 patients of HIV with TB co infection after 2 months of antituberculous treatment received antiretroviral. The most common regimen was stavudine/zidovudine + lamivudine + Efavirenz owing to presence of rifampicin in AKT. All patients had their tuberculin testing done with standard 0.5ml of PPD (purified protein derivative) and it was negative in all patients prior to star of ART.

On serial follow up at the interval of 1 month, 5 out of 40 patients were found to develop immune reconstitution as per the definition.

Table 2 Clinical profile of patients who developed immune reconstitution
Baseline Mean CD4 count of these 5 patients was 58.6/cmm. Baseline mean CD4 count of remaining 35 patients who did not show immune reconstitution was 184/cmm. This difference was significant (p value<0.01)

Interestingly all patients with symptomatic worsening had turned their tuberculin test turned strongly positive. Rest 35 patients continued to have negative tuberculin test. Mean time interval to develop immune reconstitution and conversion of tuberculin test was 31 days from the start of ART. Relevant laboratory investigations done to rule out treatment failure, other HIV related illnesses were negative. These patients were kept under close observation without stopping or changing either antituberculous treatment or ART. Complete resolution was observed subsequently.

DISCUSSION
Immune reconstitution is recognized as a potential complication that can occur after antiretroviral therapy. In general, the clinical benefits of HAART have been attributed to the decrease in HIV replication and increased T cell numbers, but its full effects on cellular immunity are still poorly understood. Studies have shown evidence of antigen-specific immune reconstitution.(3)

Estimated frequency of such response is approximately 10% to25%. Mycobacterial antigens are frequently implicated representing almost one third of all reported cases. Other such infections include cryptcocci, cytomegalovirus, HBV, HCV. Many of the clinical presentations seen in patients with untreated TB are mediated by the host's immune system.

We described patients with TB and HIV who developed exacerbations or new occurrence of some symptoms soon after the initiation of ART. The reactions included fever, appearance of lymphadenopathy, radiological worsening. Close differential diagnosis were treatment failure, drug fever, development of non tuberculous HIV related conditions. These were ruled out after extensive work up.

Proposed criteria for immune reconstitution

Major criteria
A. Atypical presentation of opportunistic infection in patients responding to ART
E.g. Exaggerated inflammatory reactions

– Fever with exclusion of other causes
–formation of other granulomas, necrosis – Enlargement of pre existing lesions
B . Decrease in plasma HIV RNA by>1log10 copies

Minor Criteria
1. Increase in CD4 count
2. Increase in immune response specific to relevant pathogen
3. Spontaneous resolution of disease with continuation of ART

Diagnosis – Presence of both major criteria or one major and two minor criteria

Immune reconstitution is attributed to strengthening of host's delayed hypersensitivity response, decrease in suppressor mechanism, and/or an increased exposure to Mycobacterial antigens following bactericidal chemotherapy. Philips and coworkers described the emergence of clinical lymphadenitis and cutaneous lesions secondary to mycobacterium avium after start of ART. French and coworkers have previously observed that HIV patients treated with ART may regain delayed type of hypersensitivity to various skin antigens (4). Restored skin test reactivity may be an indication of enhanced T cell function independent of CD4 cell count and has major clinical importance. Given the atypical and sporadic presentation of immune reconstitutions, their anticipation by restoration of tuberculin test may prove helpful in managing these reactions. Also those

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patients having their nadir CD4 count below 75/cmm deserve special attention after ART with respect to immune reconstitution (5).

SUMMARY

A paradoxical exacerbation of tubercular signs and symptoms occur after ART. This immune reconstitution is associated with enhanced skin reactivity. A thorough work up is required before a diagnosis positive restoration due to immune reconstitution is made. However it is important that treating clinician be aware of this phenomenon which simply represents an enhanced immune response to Mycobacterial antigens. In this case no change or discontinuation of treatment is required. If severity of symptoms is more, short term steroids while maintaining ART may prove helpful. Importantly, tuberculin test may prove a simple, easily accessible tool to predict this somewhat underestimated but clinically significant phenomenon.

Table 1 Extrapulmonary sites were

site	Number
abdominal	8
pleural	2
Peripheral lymphadenopathy	5
CNS- TB meningitis, tuberculoma	2
Total	17

Table 2 Clinical profile of patients with immune reconstitution

Sl.. No	SITE of TB	Age /sex	CD4 Cnt	TT before ART	WHO Class	CDC Stage	Inv. Before treatment	TT on follow up	Investigation during follow up
1	Disseminated	38yrs/M	120	Neg	IV	C3	TLC-5200, ALC-1282, CXR-Left Pl.effusion, USG abd. HS-megaly & abdominal lymphadenopathy. Pl. fluid S/O tuberculosis Biopsy of LN S/O Tubercular lymphadenitis.	Positive	LN enlargement, Biopsy s/o Reactive Lymphadenitis, CD4-154. X-ray and USG no worsening
2	Pulmonary & Abdominal	47yrs/M	35	Neg	IV	C3	TLC-8500, ALC-2734, CXR-Miliary TB.USG Abdomen-lymph node at porta hepatis, mesenteric nodes with thickened mesentery & omentum, sp. AFB-negative.	Positive	CXR-Resolution USG Abdomen-Ascites. Ascitic fluid R/M-Pr.-3 gm%. sug-60mg%.20 NC-10L & 10N.
3	Abdominal	35yrs/F	22	Neg	IV	C3	TLC-5000, ALC-1650.CXR-Normal, USG abd.-Multiple abdominal LNpathy with splenic microabscess.	Positive	CXR-Right apical infiltrations.Sp.AFB- Neg. USG- Mild spleenomegaly with LNpathy.
4	Pulmonary	25yrs/M	20	Neg	III	B3	TLC-5000, ALC-1500, CXR-B/L-Basal Infiltrates.Sp. AFB positive. USG-Abdo- Normal Study.	Positive	CXR-Right minimal pl. effusion. C/O –Cough, Breathlessness Sp. AFB-Neg.

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5	Abdominal	22yrs/F	96	Neg	IV	C3	TLC-4600, ALC-1288,CXR-Normal,USG abdomen- Normal.	Positive	After starting ART Patients has developed previous USG abd. Para aortic & pre aortic LNpathy with splenic microabscess.

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