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PULMONARY TUBERCULOSIS IN HIV POSITIVE INDIVIDUALS: PRELIMINARY REPORT ON CLINICAL FEATURES AND RESPONSE TO TREATMENT*

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Summary:

Objectives: To study the clinical, radiological and immunological profile of pulmonary tuberculosis in HIV infected patients and assess the response to short-course chemotherapy regimens.

Methods: Seventy eight patients (68 males and 10 females) with HIV infection and having symptoms suggestive of tuberculosis attending the Government Hospital for Thoracic Medicine, Tambaram or the Tuberculosis Research Centre, Chennai were studied. The diagnosis of tuberculosis was based on clinical evaluation, bacteriological examination including sputum smear and culture and chest skiagram. HIV diagnosis was based on two tests (rapid/ELISA), detecting different antigens. CD4+ T cell counts were done on all patients initially and at the end of treatment.

Blood tests and skiagrams were repeated at 2 months and at the end of treatment. All the patients were treated with standard (RNTCP) short course regimens. Patients were given all the doses under supervision during the initial intensive phase and through community DOTS providers in the continuation phase.

Results: Sixty five patients had culture confirmed pulmonary tuberculosis, of whom 54 had smear positive disease, initially. The radiological manifestations were varied, with 11 subjects having miliary tuberculosis, 54 with non-homogeneous opacities and 10 with cavitation. The mean CD4 cell count at intake was 192 ± 172 cells/cumm. Patients showed good initial response to treatment with significant weight gain. At the end of 2 months of treatment, 91% of patients had sputum cultures negative for *Mycobacterium tuberculosis.* However, the CD4 % fell significantly by the sixth month. The study is being continued to assess the long-term response to SCC of patients with HIV and tuberculosis.

Conclusions: Tuberculosis has a varied clinical presentation in patients with HIV infection. The spectrum of radiographic features ranges from normal to a miliary pattern. Inspite of clinical and bacteriological improvement during treatment, immunologic deterioration may continue.

Key words: Pulmonary tuberculosis, HIV infection, Clinical profile of TB/HIV patients.

INTRODUCTION

HIV infection has increased the burden of tuberculosis, especially in populations where HIV has become common, and where the prevalence of tuberculosis infection is high [1,2]. It is estimated that worldwide, nearly two billion people are infected with *Mycobacterium tuberculosis,* 36 million are HIV infected and over 10 million are dually infected with *M.tuberculosis* and HIV. Tuberculosis is the commonest opportunistic infection occurring among HIV positive persons in India and it is estimated that 60-70% of HIV positive persons will develop tuberculosis in their lifetime[3]. Several studies from different parts of the country have also documented high HIV sero-prevalence rates among tuberculosis patients[4].

Diagnosis of tuberculosis among HIV infected persons is often delayed, and is difficult to make since HIV-infected persons with tuberculosis are more likely to have negative sputum smears and minor or non-specific X-ray abnormalities[5]. Among HIV infected persons with an intact immune system, the clinical features of tuberculosis are fairly typical; however, these change markedly among HIV-positive persons with severe immunodeficiency (e.g.CD4 cell counts <200).

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The aim of this study was to record the clinical, radiological and immunological profile of pulmonary tuberculosis in HIV seropositive persons. This preliminary report is part of a larger ongoing clinical trial to evaluate the efficacy of short course intermittent (RNTCP) regimens in patients with HIV and tuberculosis.

METHODS

HIV sero-positive patients with symptoms suggestive of pulmonary tuberculosis attending the Outpatient Departments at Tuberculosis Research Centre, Chennai (TRC) and Government Hospital for Thoracic Medicine (GHTM), Tambaram were enrolled, if they fulfilled the inclusion criteria. The patients had to be more than 15 year old, residing in an area within 100 kms from TRC or GHTM and had to have no major systemic derangement which could cause difficulty in management. Informed consent was taken from the patients prior to enrolment into the study. A detailed history including previous anti-tuberculosis therapy, addictions & high-risk sexual behaviour was elicited. A general clinical examination was performed. Baseline investigations such as chest X-ray, 3 sputum specimens for AFB smear, culture and drug sensitivity and blood examination were performed as detailed below. Tuberculin testing was done with 1TU of PPD RT 23 and the induration was measured after 48 to 72 hours by trained readers.

The sputum smears were examined for AFB by fluorescence microscopy. The sputum specimens were processed by modified Petroff's method and cultured on the LJ medium. Positive cultures were subjected to identification tests, viz Niacin production, growth on LJ medium containing 500 mg/L of para-nitro benzoic acid and stability of Catalase at 68°C in order to identify the organism as *Mycobacterium tuberculosis* or non-tuberculous mycobacteria. All the positive cultures were subjected to drug susceptibility tests using standard methods as described elsewhere[6]. HIV screening was performed using the Tridot Rapid Test; all positive results were confirmed using Comb Aids Rapid test and also by ELISA. Hemoglobin, total and differential leucocyte cell counts, blood sugar, blood urea, serum creatinine, serum uric acid and liver function tests were performed. The CD4, CD8 cell counts and CD4/CD8 ratio were determined using flow cytometry (Simultest-IMK Lymphocyte kit).

The diagnosed patients were started on anti-tuberculosis (RNTCP) regimens based on history of previous ATT and the current sputum smear results. Regimens used were Cat I: 2H3R3E3Z3/4H3R3, Cat II: 2S3H3R3E3Z3/1H3R3E3Z3/5H3R3E3 and Cat-III: 2H3R3Z3/4H3R3. Standard dosages were used and managment of adverse reactions was done according to RNTCP guidelines. Treatment was completely supervised during the initial intensive phase and community DOTS providers were arranged for those patients unable to attend the clinic as required during the continuation phase. All the patients underwent periodic monthly clinical and sputum examination till the end of treatment, at which time the clinical, radiological, bacteriological and immunological parameters were re-evaluated.

RESULTS

Of the 78 patients included in this report, 68 (87%) were males and 10 (13%) were females. Nearly one half of the patients were 31-40 years old while 35% were 20-38 year old; 52 (67%) patients were married and living with their spouses, 9 (11%) were either widowed or separated from their spouses and 17(22%) were unmarried. Of the 68 males, 56 (82%) admitted to having sexually high risk behaviour, 3(4%) had history of blood transfusions and 1 patient was an intravenous drug abuser. All the females, except one, got the infection from their husbands. Most of the patients had a combination of two or more symptoms at the time of enrolment. The frequency of the salient symptoms as reported is given in Table 1. The mean duration of the salient symptoms prior to reporting was 12 weeks.The salient clinical findings at the time of enrolment are given in Table 2. Oral thrush and generalized muscle wasting were prominent features. The tuberculin test results were available for 59 patients and the distribution is given

in Table 3; 56% had a reading < 5mm. One notable finding was that 7 patients had indurations more than 20mm.

Table 1: Distribution of symptoms* (N=78)

Symptoms	Number	%
Cough	76	97
Weight loss	73	94
Fever	62	79
Dyspnoea	53	68
Chest pain	37	47
Hemoptysis	14	18

*Patients had more than 1 symptom each

Table 2: Distribution of clinical signs (N=78)

Signs	Number	%
Muscle wasting	37	47
Oral thrush	30	38
Lymphadenopathy	23	29
Clubbing	14	18
Pedal oedema	7	9
Respiratory Signs		
Bronchial breathing	11	14
Rhonchi	11	14
Crepitations	43	55

The pre-treatment chest X-rays were available for 66 patients; of these, 12 patients had more than 1 radiological lesion (Table 4).

Outcome of treatment

During the course of anti-tuberculosis therapy,several parameters were evaluated. The mean weight at enrolment was 41.5 ± 8 kg; the median weight was 40 kg with a range from 30 kg to 73 kg. By the end of treatment, there was a significant weight gain with the mean weight increasing to 48 kg.

Of the 78 patients, 56 were started on RNTCP Category I, 15 on Category II and 7 on Category II regimens. In all, 65 patients had positive pre-tretment sputum culture; 54 (83%) patients were sear positive and 11 were smear negative. The oerall smear conversion rate by the end of the second month of treatment was 70% and culture conversion was 91%. The smear conversion on a monthly basis is shown in Figure 1.

Table 3: Distribution of Mantoux test indurations (N=59)

Induration	Number	%
0 mm	25	42
1-5 mm	8	14
6-10 mm	2	3
11-20 mm	17	
29>20mm	7	12
Total	59	100

Table 4: Radiological lesions at presentation*

Lesion	Number	%
Normal X-ray	6	9
Pleural effusion	8	12
Mediastinal glands	2	3
Pneumothorax	1	2
Opacities		
Focal U/L	6	9
Focal L/L	9	14
Extensive	25	38
Cavitation		
U/L	7	11
L/L	2	3
Miliary tuberculosis	11	17

*12 patients had more than one lesion

The comparison of the immunological parameters at the time of intake and at completion of treatment is shown in Table 5. The mean CD4 cell count at intake was 192 + 173 cells/cu.mm with a range of 16 to 918. There was a progressive decline in the CD4%, CD8% and the CD4/CD8 ratio at the end of treatment.

DISCUSSION

Tuberculosis is the commonest opportunistic disease in HIV positive persons in India

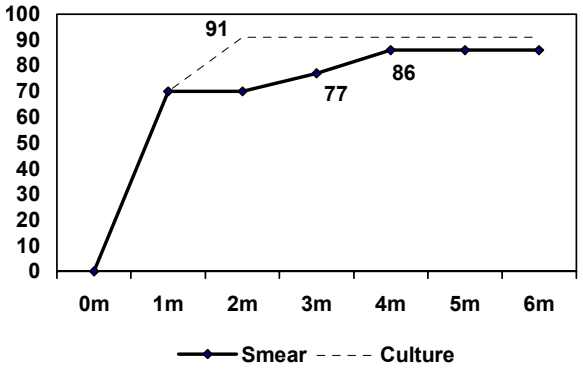

Figure: Sputum smear and culture conversion during treatment

and can develop at any stage of the disease. Many studies have given the clinical profile of tuberculosis in HIV positive persons in USA and Africa[2,7]. However, there is a paucity of such data from India[8,9]. Hence, it is important to study their profile, as it would help in making an early diagnosis. It is also important to study the efficacy of short course intermittent regimens in this group, as the RNTCP strategy covers all patients irrespective of their HIV status[5] .

The most common presenting symptoms were cough and loss of weight, followed by fever. The average duration of symptoms was 12 weeks, indicating that there was a delay in diagnosing tuberculosis and starting treatment. Whether the delay was at the patient or provider level needs further investigation. Half the patients were emaciated and 40% had associated oral thrush, which serves as a good clinical pointer towards HIV infection. About 30% of patients had an associated extra-pulmonary focus in the form of cervical or axillary lymphadenitis, pointing to the disseminated nature of the disease in HIV positive persons. Half the patients had tuberculin reaction > 5mm but there was no correlation between CD4 counts and Mantoux reaction.

The radiological manifestations were varied with the commonest lesion being exudative opacities, which were found in 51% of the patients. Lower lobe lesions were more common and the disease quite often tended to involve more lung fields in both lungs. Only 14% of patients had cavitary lesions. Miliary tuberculosis was the presentation in 17% of the patients and 9% had normal X-ray in spite of having positive sputum cultures. Previous studies have also reported a lower prevalence of focal infiltrates, upper lobe infiltrates and cavitary disease in HIV+ patients with tuberculosis[7]. Hence, the diagnosis of tuberculosis has to be suspected in HIV positive persons irrespective of the type, site and extent of radiological lesions. Further, since tuberculosis could be present even in persons with a normal chest X-ray, the presence of symptoms warrants detailed investigations.

Of the 65 cases, who had culture confirmed pulmonary tuberculosis, 83% were smear positive at intake. This is not very different from the situation in HIV un-infected tuberculosis patients and indicates that smear microscopy could be a sensitive diagnostic tool even in the presence of HIV infection. However, a study from New York found that smears were AFB positive more often in non-HIV-infected patients with pulmonary

Table 5: Immunological parameters at start and end of treatment (N=78)

	0 month	End of treatment	P value
Lymphocyte count (cells/cu.mm)	2588 + 1100	2162 +1694	P < 0.05
CD4%	14.3 + 8.3	9.9 + 6.7	P<0.001
CD4 count (cells/cu.mm)	192 + 172	199 + 214	NS
CD8%	56.3 + 14.1	47.9 + 15.2	P<0.01
CD8 count (cells/cu.mm)	747 + 536	803 + 709	P=0.01*
CD4/CD8 ratio	0.33 ± 0.46	0.24 + 0.25	P<0.05

*t test was performed after log transformation NS = Not significant

tuberculosis than in HIV-infected patients[7]. In our study, smear and culture conversion rates at 2 months were 70% and 91% respectively, indicating good initial response to the intermittent short course regimens used. Patients also showed significant clinical improvement and weight gain during therapy. However, long term follow up is required to study relapse rates before the efficacy of these regimens in HIV positive persons can be established, in Indian conditions.

Patients in this study had a mean CD 4 count of 192 cells/cu.mm at baseline, indicating advanced HIV disease. Median CD4 cell counts in previous reports of tuberculosis in HIV-infected patients have ranged from < 150/cu.mm to > 300/cu.mm[10-12]. Our study also demonstrates a significant decline in CD 4 %, CD 8 % and CD 4/CD 8 ratio at the end of treatment, compared to initial values. This indicates progressive immunosupression and is a poor prognostic factor. It is known that tuberculosis accelerates HIV disease progression because of production of cytokines like TNF-a, which increase viral replication. One-year mortality for HIV/TB patient has been reported to be in the range of 20-35%[13-15]. The higher mortality in HIV+ patients who develop tuberculosis is mostly due to other opportunistic infections, which occur in the presence of profound immunosuppression.

Treatment with standard anti-tuberculosis regimens using DOTS could go a long way in improving the clinical condition and quality of life of patients with HIV and tuberculosis. However, without concomitant anti-retroviral treatment there is continued immunologic deterioration and progression of HIV disease. More data are required on the efficacy of short course intermittent regimens and their long-term outcome including mortality in these patients.

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LEAVES FROM HISTORY - 13

NGOs & Philanthropists in the vanguard of Anti-TB Movement in India

Mention has been made of some missionary and philanthropic agencies in the previous instalment of this series (*Leaves from History-12*). However, the list was by no means exhaustive and there have been several others who contributed to the cause.

Prominent among these was the Ramakrishna Mission, which added provision of services to tuberculosis patients to their multifarious relief activities, as early as 1933, in Delhi. The Ramakrishna Mission Free TB Clinic started functioning in a small rented building in the old city of Delhi and after relocating twice, finally moved to its present premises in 1948. Almost from the beginning, the Clinic was equipped for carrying out operations such as Artificial Pneumothorax, phrenectomy, etc. Basic laboratory and radiological facilities were also available and all tests were done free of charge. To make home treatment effective, some health visitors were also employed to visit patients' houses and give preventive advice.

Swami Sharvananda, Dr. I.T. Mittra, Dr. N.C. Joshi, Dr. S.C. Sen and Dr.S.K. Sen were among the pioneers who nurtured the institution in its early years.

Nor was this the only non-governmental activity going on in the country. Anti-Tuberculosis Sub-Committees had been formed in Bangalore, Calcutta, Madras, Jullundur & Ludhiana and nine cities in UP in the middle thirties with official help although a record of their activities is not currently available. It is also of interest to note that the Bengal Tuberculosis Association (established 1928) & the UP Tuberculosis Association (March 1939) predate the formation of the Tuberculosis Association of India (1939) and sought affiliation only subsequently. The early activities of the Bengal TB Association included health education, publication of a monthly journal, running of dispensaries in Calcutta & Howrah and rendering of assistance to several others in Bengal & training of TB health visitors. The Association had the benefit of advice from such stalwarts as Dr.B.C. Roy, Dr.A.C. Ukil and Dr.S. Sarbadhikari. The UP Tuberculosis Association carried out a Tuberculin Survey as early as 1939.