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ABSTRACT

Background: An increase in tuberculosis (TB) incidence has been associated with human immunodeficiency virus (HIV). Aims: To describe the clinical characteristics and treatment outcome of patients with HIV and miliary TB treated with short-course intermittent chemotherapy in the absence of access to highly active antiretroviral therapy (HAART).

Settings and Design: Prospective study of HIV infected adults referred to a TB clinic between July 1999 and July 2004.

Materials and Methods: On diagnosis of miliary TB, patients were treated with a standard regimen of two months of isoniazid, rifampicin, ethambutol and pyrazinamide followed by four months of isoniazid and rifampicin (2EHRZ/4RH3) thrice weekly and followed up for 24 months. Patients were reviewed clinically every month and two sputa were collected. Chest radiographs and blood investigations were done at two months, end of treatment and every six months thereafter.

Results: Of 498 patients with HIV and tuberculosis, 31 (6%) were diagnosed as miliary tuberculosis. At diagnosis, sputum smear was positive for acid-fast bacilli (AFB) in 14 patients (45%) and Mycobacterium tuberculosis was isolated in 21 (68%). The mean CD4 cell count was 129 ± 125 cells/mm³. Twenty-five patients were declared cured at the end of treatment (81%) while one (3%) died and five (16%) failed. The recurrence rate was 19.4/100 person-years and the median survival was 17 months (95% CI 14 to 20). None of the patients received antiretroviral therapy.

Conclusions: Miliary TB tends to occur among HIV infected patients with severe immunosuppression. Though the initial response to short-course chemotherapy was encouraging, a high recurrence rate and mortality was observed indicating poor prognosis in HIV.

KEY WORDS: Human immunodeficiency virus, miliary tuberculosis, short-course chemotherapy
(extrapulmonary TB) by AFB smear and mycobacterial culture along with supportive clinical and radiographic features.

The HIV testing was performed after pre-test counseling and obtaining an informed written consent. The diagnosis of HIV infection was based on three positive tests (two rapid tests - Tridot, J. Mitra and Comb AIDS, Span Diagnostics, India - followed by an ELISA (Labsystems, U.K). Blood hematology, biochemistry and CD4/CD8 cell counts (by Beckman Coulter Epics Altra flow cytometry) was also performed.

The HIV positive adults with evidence of TB, willing for home visits and willing to sign an informed consent were included in the study. Pregnant women, patients in moribund condition and with serious associated illnesses or unwilling to attend the clinic as required were not included in the study. During the study period, eligible HIV positive patients with TB were enrolled into the HIV-TB chemotherapy trial and started on antituberculosis treatment (ATT). The Institutional ethics committee approved the study and written informed consent was obtained from the participants. All patients were treated with a standard short-course intermittent regimen (as recommended by the Revised National Tuberculosis Control Program) consisting of two months of intensive phase with Ethambutol 1200 mg, Isoniazid 600 mg, Rifampicin 450/600 mg (based on body weight) and Pyrazamide 1500 mg, all given three weekly. This was followed by four months of continuation phase with Isoniazid 600 mg and rifampicin 450mg/600mg administered three times a week. In addition, Pyridoxine 10 mg was administered on treatment days. All doses were supervised in the intensive phase (Directly Observed Treatment (DOT)); thereafter they were supervised once a week in the continuation phase.

Patients were followed every month till the end of treatment. During monthly visits a clinical examination was done and three sputum specimens were collected for AFB smear microscopy and culture. Chest radiographs and blood tests were repeated after two months of ATT and at the end of treatment. After treatment completion, patients were followed up for 24 months. Clinical examination was done every month and two sputum specimens were collected for smear microscopy and culture. Blood tests and chest radiographs were done once in six months or earlier if patients developed symptoms suggestive of recurrence of TB. The chest X-rays were read by two medical officers involved in patient management. In case of any discrepancy it was read by a qualified independent assessor.

Among the patients enrolled into the TB chemotherapy trial, criteria for diagnosing miliary TB were the presence of miliary pattern on chest radiograph or evidence of multi organ involvement, along with one or more of the following features: 1) clinical features compatible with TB including cough for two weeks or more, fever, weight loss, night sweats, loss of appetite or hemoptysis 2) Positive smear or culture for TB, 3) histopathological evidence of TB.

The medical records of all patients were examined for patient characteristics, clinical features, results of investigations, treatment regularity, complications and outcome.

Outcome definitions:[9]

- **Cure:** Patients were considered cured of TB if they had completed treatment and had all negative sputum cultures during the last two months of treatment.
- **Recurrence:** A patient declared cured of TB who developed another episode of bacteriologically confirmed TB during follow-up, was considered as recurrence of TB.
- **Deaths:** Deaths were classified as being due to TB if one or more sputum cultures were positive or there was evidence of TB at some other site, at the time of death.

Data was analyzed using SPSS software (v. 11, Chicago, Illinois, USA). Paired Student’s t-Test was used to compare differences between baseline and post-treatment. The Kaplan-Meier Survival analysis was used to plot survival versus time in months.

Results

A total of 498 patients with TB and HIV co-infection were seen during the study period. Thirty-one (6.2%) patients met the criteria for miliary TB of whom 27 were males and four were females. The mean weight was 43.0 ± 7.7 kg and mean age 34.3 ± 8.5 years.

Clinical features: Predominant symptoms at presentation included weight loss (n= 29 {94%}), cough (n= 26 {84%}) and fever (n= 25 {81%}). Clinical examination revealed coexisting oral thrush (n=18 {58%}), enlarged cervical or axillary lymph nodes (n=17 {55%}) and clubbing (n=9 {29%}). Lung signs in the form of crepitations or decreased breath sounds were seen in 68% (n=21) of our patients. At presentation miliary mottling was a consistent finding in all the chest radiographs. Mantoux test was positive (>5 mm) in 12 patients with a mean induration of 5.1 mm. Anemia was a common finding (70%) and lymphocyte count, lymphocyte percentage and CD4 cell count was <150 cells/mm³ in 22 patients. Fourteen patients had at least one sputum smear positive for AFB. While 21 (68%) patients had *Mycobacterium tuberculosis* grown in sputum culture, 10 (32%) were culture negative.

Figure 1 shows the sputum smear and culture status of all patients at 0 and six months. Twenty-five patients were declared bacteriologically cured at the end of treatment (81%) while one died and five failed to treatment (two were culture positive and three required a change of treatment on clinical grounds). A significant increase was observed in hemoglobin, lymphocyte count, lymphocyte percentage and CD4 cell count but no significant change was noted in CD4% among the 25 patients in whom paired results were available [Table 1]. There was a complete resolution of the miliary pattern in the chest radiographs at the end of treatment in 24 patients. Minimal residual lesion was seen in three and fibrosis in one patient. Chest radiograph showed deterioration in one patient and persistent miliary pattern was seen in one patient after six months of ATT.

Follow-Up: All the 25 patients, declared cured at the end of ATT were followed up for two years post treatment. Four patients died due to a variety of reasons including diarrhea, wasting,
neurological complications and/or non-tuberculosis pulmonary infections. Of the remaining 21 patients, eight patients developed recurrence of TB at different time points during follow-up: six between six and 12 months and two between 12 and 24 months of completion of ATT. The recurrence rate was 19.4/100 person-years. Of these eight recurrences, four died subsequently during re-treatment. The median survival time after diagnosis was 17 months (95% CI 14 to 20 months). Of the nine deaths in our study population, five deaths were directly related to TB, including one during initial treatment.

**Discussion**

Clinical experience in treating HIV-associated TB with standard short-course chemotherapy suggests that the response is initially favorable, usually resulting in rapid resolution of symptoms, clearing of radiological abnormalities and sterilization of sputum cultures at the same rate as in HIV seronegative patients. However, there are not many studies describing the clinical characteristics and response to short-course intermittent therapy for miliary TB in HIV positive individuals. In this study, we found 6% of HIV-TB patients presenting with miliary pattern, consistent with another report from the same region. The most common presenting complaints were weight loss followed by cough and fever as in seronegative patients. More than 50% had anemia and oral thrush, which serves as a good clinical pointer towards advanced HIV disease. All patients had classical miliary mottling, both coarse and fine patterns, on chest radiographs. Miliary TB can also have atypical presentations in the form of cryptic miliary TB and acute respiratory distress syndrome.

Of the 31 patients, 22 had CD4 cell counts <150 cells/mm³ at presentation. Our findings are similar to that of Lado et al., where the mean CD4 cell count of HIV-miliary TB patients was 148 cells/mm³, lower than in all other forms of tuberculosis. A study done at our Institute found that patients with HIV and pulmonary tuberculosis had a mean CD4 cell count of 192 cells/mm³. The low CD4 cell counts in the present series indicate that miliary TB is associated with severe immunosuppression in HIV positive persons.

In our series, we had a high yield of *Mycobacterium tuberculosis* on sputum culture contrary to few previous reports. In HIV uninfected miliary TB patients, smear positivity of 37% and culture positivity of 90% (predominantly in sputum and bronchial lavage specimens) have been reported. High yield of *Mycobacterium tuberculosis* has also been demonstrated from liver biopsy and bone marrow specimens in patients with miliary TB. Our experience indicates that it is possible to get a high yield of *Mycobacterium tuberculosis* from sputum, even in miliary TB, when the laboratory is well standardized and multiple specimens are collected. Another possible reason for this high smear and culture positivity in our patients could be the presence of a high degree of immunosuppression resulting in poor granulomatous reaction and reduced ability to contain bacilli. It is possible that the miliary tubercles were more “loose meshed” than those of HIV negative tuberculous miliary granulomata.

Good response to a six-month intermittent ATT was seen in 81% of our patients, manifested by significant clinical, bacteriological and radiological improvement. The course of the chemotherapy was uneventful without any adverse reactions to the anti-tuberculosis drugs. However, the long-term outcome of these patients with advanced HIV disease (mean CD4% of 10.5 and CD4 count of 129 cells/mm³) was poor in spite of successful anti-TB therapy. Despite an increase in the percentage and absolute count of lymphocytes, the CD4% did not show a significant rise, indicating that anti-TB treatment alone does not improve immune status. The recurrence rate was high, with about a third of patients developing recurrence within two years of completing therapy. This high recurrence rate in our series could be due to the advanced stage of HIV disease with the majority of patients having a CD4 cell count of less than 150 cells/mm³, as TB recurrence is known to occur more frequently among severely immunocompromised patients. Secondly, treatment was not fully supervised in the continuation phase in our study as we followed the RNTCP guidelines of once a week and
supervision and concealed irregularity is a possibility. Another possibility is re-infection due to exposure to TB in the hospital environment as the majority of our patients were admitted for various reasons and we exposed to other sputum positive TB patients in the ward. Several studies in sub-Saharan Africa have shown an increased rate of TB recurrences due mostly to re-infection in HIV infected patients as compared to HIV negative TB patients. Studies from Kenya, Zaire, Zambia etc. have documented recurrence rates among HIV-infected TB patients varying from 16 to 22 per 100 person-years. Our results are in agreement with these African studies.

Further, a higher mortality rate of 29% was observed in our group as compared to 18-20% in seronegative miliary TB patients, with a median survival time of only 17 months from the time of diagnosis. This is not surprising, given the advanced stage of the HIV disease in the present study and the non-availability of antiretroviral drugs. This study was done prior to the rollout of free antiretroviral treatment in India and none of these patients could afford to purchase drugs from the market. Almost 50% of deaths in our study were due to AIDS-associated opportunistic infections. Although there was no direct evidence of TB in these patients at the time of death, underlying TB could not be excluded completely (autopsies not performed, which is one of the limitations of our study).

In summary, miliary TB has become a more common form of presentation of TB, in the HIV era.

High yield of Mycobacterium tuberculosis from sputum of patients with miliary TB can be obtained, if the laboratory is standardized and multiple specimens are collected. In spite of adequate anti-TB treatment and bacteriologic response the overall prognosis of miliary TB is not encouraging due to high recurrences and mortality and it can be considered a poor prognostic feature in people living with HIV/AIDS. The WHO guideline recommends starting ART two to eight weeks after ATT in patients with HIV and TB with a CD+ cell count < 200 cells/mm³. Though this is a controversial issue, ongoing research to determine the optimal time to initiate ART in HIV associated TB will provide evidence on this issue in the years to come. In the absence of ART, it would probably be advisable to continue ATT for a longer period or consider secondary prophylaxis for TB, in order to reduce recurrence rates. Further research is required to ascertain whether a longer course of anti-tuberculosis treatment or HAART or both are necessary, for patients with HIV and miliary TB.