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HIV-tuberculosis co-infection in an Indian scenario: The role of associated evidence of immunosuppression

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ABSTRACT

Objective: To determine the relationship between tuberculosis and the degree of immunosuppression as determined by CD4 count. The impact of immunosuppression on the severity of tuberculosis was also studied. **Methods:** A retrospective analysis was performed in patients newly diagnosed with HIV infection and antiretroviral therapy (ART)-naive patients with known HIV seropositivity. All patients were diagnosed with active tuberculosis between January 2008 and December 2010, based on review of their medical records. Patients on chemoprophylaxis for opportunistic infection were excluded. Pattern and severity of tuberculosis, associated stigmata of immunosuppression, and CD4 counts were noted. **Results:** Of 140 patients satisfying the inclusion criteria, 52 had mild tuberculosis with no other evidence of immunosuppression, 52 had tuberculosis of variable severity with associated evidence of immunosuppression, and 36 had severe tuberculosis with no other evidence of immunosuppression. The CD4 count was highest in the first group [(109.2±99.9) cells/ μ L] and least in the second group [(58.4±39.8) cells/ μ L], and the difference was statistically significant (P=0.004). No statistical difference was observed in the CD4 count between those with mild tuberculosis and those with severe tuberculosis. **Conclusions:** In developing countries with a high prevalence of tuberculosis in the general population, the possibility of incidental tuberculosis in patients with HIV should always be considered. CD4 count does not appear to influence the severity of tuberculosis. The presence of concomitant evidence of immunosuppression in the form of category B and C conditions is indicative of underlying immunosuppression and associated with a significantly lower CD4 count.

1. Introduction

The global pandemic of human immunodeficiency virus (HIV) infection has led to a dramatic upsurge in the prevalence of tuberculosis[1]. The rise in annual incidence of tuberculosis worldwide from an estimated 4 million in the pre-HIV era[2] to nearly 10 million in the post-HIV era[3] is a testimonial to the impact of HIV on tuberculosis. Tuberculosis is now one of the principal opportunistic infections seen in people living with HIV infection, and it is also a major cause of morbidity and the largest cause of mortality in this population[4]. Over one quarter of all acquired immunodeficiency syndrome (AIDS)-related deaths are now attributable to tuberculosis[5]; of these deaths, 99% occur in the developing world[6]. HIV infection is the single most powerful risk factor for an individual to develop tuberculosis in his lifetime[7]; the lifetime risk of contracting tuberculosis in an HIV-positive individual is 30% or more as compared to 5%-10% in an HIV-negative individual[8].

The central mechanism behind this augmented risk is of course immunosuppression, resulting principally from HIV induced CD4 lymphocyte destruction. Other mechanisms include CD8 lymphocyte depletion[9], up-regulation of *Mycobacterium tuberculosis* (*M. tuberculosis*) entry receptors on macrophages[10], manipulation of macrophage bactericidal pathways by HIV[11], impairment of chemotaxis[12], altered Th1/Th2 balance[11] and diminished tumor necrosis factor (TNF)-mediated apoptotic response to *M. tuberculosis* infection[13].

Impaired cell mediated immunity immediately hampers the body's principal defense against both new infection

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with *M. tuberculosis* and reactivation of latent infection. This mechanism is also responsible for most of the other opportunistic infections seen in HIV-infected individuals. However, tuberculosis differs from these infections in that it is widely seen within the general population, especially in the developing world. Indeed, immunocompetent individuals constitute the majority of persons with active tuberculosis in these regions. This is one of the reasons why tubercular infection can occur at any level of CD4 count. An unspoken corrigendum of this fact is that taken alone, tuberculosis does not necessarily indicate immunosuppression in a given individual with HIV seropositivity.

In addition to its impact on the risk of developing tuberculosis, HIV infection also influences the manifestation of tuberculosis. Extrapulmonary tuberculosis has been shown to occur with a higher frequency among HIV positive individuals as compared to the general population[14]. Once again, atypical and extrapulmonary presentations of tuberculosis can be attributed to HIV-induced impairment of the normal immune response, resulting in rapid dissemination of infection. Needless to say, such an argument presupposes that atypical, extrapulmonary and severe forms of tuberculosis should occur in persons with greater degrees of immunosuppression and correspondingly lower CD4 counts-a finding which is yet to be confirmed by large scale studies.

This study was therefore designed to determine the relationship between tuberculosis and the degree of immunosuppression as determined by CD4 count and to explore the impact of additional clinical evidence of immunosuppression in the form of category B and C conditions. A secondary objective was to test the hypothesis that lower CD4 counts are associated with atypical, extrapulmonary and severe forms of tuberculosis.

2. Materials and methods

2.1. Study settings

Kasturba Medical College (Manipal, India) is a major tertiary care centre in Southwestern India. The catchment area of this hospital corresponds to the district of Udupi in which it is located, along with the neighbouring districts of Uttara Kannada and Dakshina Kannada. The combined population of this region approximates 4.36 million individuals.

2.2. Patients

A retrospective analysis was performed in patients newly diagnosed with HIV infection and antiretroviral therapy (ART)-naive patients with known HIV seropositivity, who were diagnosed with active tuberculosis between January 2008 and December 2010, based on review of their medical records. Patients on chemoprophylaxis for opportunistic infection were excluded.

2.3. Diagnosis and typing of tuberculosis

All patients were diagnosed with tuberculosis on the basis of one or more of the following criteria: sputum or tissue sample positivity for acid fast bacilli, isolation of *M. tuberculosis* in culture from sputum or tissue sample, radiological features suggestive of tuberculosis and positive skin tuberculin testing. The type of tuberculosis observed was noted for all patients. Tubercular lymphadenitis, pulmonary parenchymal tuberculosis, tubercular pleural effusion and tubercular peritonitis were considered as mild tuberculosis. Disseminated tuberculosis, *i.e.*, involvement of more than one organ/organ system, tubercular meningitis, tuberculoma and military tuberculosis were considered as severe tuberculosis.

2.4. CD4 counting

The presence of additional evidence of immunosuppression at the time of diagnosis of tuberculosis in the form of accompanying category B or C conditions[15] was also noted. CD4 counts were noted for all patients included in the study. The earliest CD4 count available for each patient that was performed at least 2 weeks after the diagnosis of tuberculosis and prior to initiation of antiretroviral therapy was considered for the purpose of the study, to avoid falsely depressed CD4 counts in acutely ill patients.

2.5. Statistical analysis

All data was analysed using SPSS Statistics version 17.0 (Chicago, USA). Continuous variables are presented as mean± SD. Independent sample *t*-test and one way ANOVA were used to compare the means of variables between various patient subsets. *P*-values less than 0.05 were considered to indicate statistical significance.

3. Results

3.1. Distribution of forms of tuberculosis across patient subsets classified according to severity of tuberculosis and evidence of immunosuppression

A total of 451 patients were either diagnosed to be HIV seropositive or known to be HIV-positive but ART-naive

and not on any form of chemoprophylaxis for opportunistic infection, during the study period. Of these patients, 140 had active tuberculosis during the study period. Fifty-two patients had a mild form of tuberculosis with no other evidence of immunosuppression (Subset A). Fifty-two patients had tuberculosis of any severity in association with other manifestations of immunosuppression (Subset B). Thirty-six patients had severe tuberculosis without any other evidence of immunosuppression (Subset C). The three subsets were comparable in baseline characteristics (Table 1).

Overall, the commonest forms of tuberculosis, *i.e.*, parenchymal pulmonary tuberculosis and tubercular lymphadenitis, were seen in 39 (27.9%) patients each, and disseminated tuberculosis was seen in 35 (25.0%) patients. The least common form of tuberculosis tubercular pericarditis was seen in only one (0.7%) patient.

Analysis across the patient subsets showed that tubercular lymphadenitis and parenchymal pulmonary tuberculosis were also the commonest forms in the subset A, seen respectively in 26 (50.0%) and 20 (38.5%) patients. In the subset B, parenchymal pulmonary tuberculosis and disseminated lymphadenitis were seen in 19 (36.5%) and 13 (25.0%) patients respectively. In the subset C, 26 (72.2%) patients had disseminated tuberculosis, while 4 (11.1%) patients had tubercular meningitis. These findings are detailed in Table 2.

Table 1

Comparison of baseline characteristics and CD4 counts between patients with active tuberculosis.

Patient subset	Age (years)	Male-to-female ratio	CD4 count (cells/ μ L)
Subset A	41.1±9.7	47:5	109.2±99.9
Subset B	38.7±7.4	36:16	58.4±39.8
Subset C	40.4±8.5	26:10	92.8±82.9

The patients in the subset A had a mild form of tuberculosis with no other evidence of immunosuppression; those in the subset B had tuberculosis of any severity associated with other manifestations of immunosuppression; and those in the subset C had severe tuberculosis without any other evidence of immunosuppression.

Table 2

Distribution of forms of tuberculosis across patient subsets.

Patient	Form of tuberculosis	Number of patients	Patient percentage (%)
Overall (n=140)	Pulmonary parenchymal tuberculosis	39	27.9
	Disseminated tuberculosis	39	27.9
	Tubercular lymphadenitis	35	25.0
	Tubercular meningitis	8	5.7
	Tubercular effusion	7	5.0
	Tuberculoma	5	3.6
	Tubercular peritonitis	3	2.1
	Miliary tuberculosis	3	2.1
	Tubercular pericarditis	1	0.7
Subset A (n=52)	Tubercular lymphadenitis	26	50.0
	Pulmonary parenchymal tuberculosis	20	38.5
	Tubercular effusion	5	9.6
	Tubercular peritonitis	1	1.9
Subset B (n=52)	Pulmonary parenchymal tuberculosis	19	36.5
	Disseminated tuberculosis	13	25.0
	Tubercular lymphadenitis	9	17.3
	Tubercular meningitis	4	7.7
	Tubercular effusion	2	3.8
	Tubercular peritonitis	2	3.8
	Tuberculoma	2	3.8
	Miliary tuberculosis	1	1.9
Subset C (n=36)	Disseminated tuberculosis	26	72.2
	Tubercular meningitis	4	11.1
	Tuberculoma	3	8.3
	Miliary tuberculosis	2	5.6
	Tubercular pericarditis	1	2.8

The patients in the subset A had a mild form of tuberculosis with no other evidence of immunosuppression; those in the subset B had tuberculosis of any severity associated with other manifestations of immunosuppression; and those in the subset C had severe tuberculosis without any other evidence of immunosuppression.

3.2. Comparison of CD4 counts between patient subsets

The mean CD4 count was highest in the patients with miliary tuberculosis and lowest in the patient with tubercular pericarditis (Table 3). No significant correlation between the CD4 count and form of tuberculosis was seen (Table 4). The mean CD4 count was significantly higher in the subset A [(109.2±99.9) cells/μL] than in the other two subsets (P=0.004). Interestingly, the subset C which presented with the most severe form of tuberculosis actually had a higher mean CD4 count [(92.8±82.9) cells/μL] than the subset B which included a proportion of patients with the mild forms of disease [(58.4±39.8) cells/μL]. Altogether, 10 (7.14%) patients had CD4 counts greater than 200 cells/μL.

4. Discussion

While the role that HIV plays in increasing an individual's risk of developing tuberculosis is clear, it is also important to note that the relationship between these two infections is bidirectional and mutually beneficial. Tuberculosis like any other opportunistic infection produces a state of continuous systemic inflammation resulting in overstimulation of the host immune system. The direct fallout is accelerated CD4 lymphocyte turnover, augmenting viral replication and thus viremia[16]. Infection of adjacent CD4 lymphocytes and macrophages within tuberculous granulomas has also been suggested as a mechanism of accelerated viral replication[17]. Finally, *M. tuberculosis* has now been shown to directly promote viral replication through activation of the HIV-1 long terminal repeat[18,19]. A natural consequence of this synergism between HIV and tuberculosis has been to label any form of tuberculosis as an AIDS defining disease in people living with HIV infection[20].

As shown by a careful review of available statistics, HIV is associated with a large proportion of tuberculosis in developed countries where the prevalence of tuberculosis was extremely low in the pre-HIV era, while the situation is quite different in South-East Asia where tuberculosis has always been prevalent in the general population. For instance, 26% of new cases of tuberculosis in the United States are attributable to HIV infection[1], whereas the corresponding figures for India, Pakistan and Bangladesh are only 5.0%, 0.3% and 0.2% respectively[21,23]. This is not unsurprising as the combined burden of new cases of tuberculosis in these three countries is 3 001 093[22,23], with the majority of patients being HIV-seronegative. In such a scenario, it is essential to determine whether tuberculosis in a given HIV-positive individual is really due to underlying immunosuppression or whether it is purely incidental. A blanket diagnosis of AIDS in HIV-positive individuals with tuberculosis would require that even HIV-positive individuals with incidental tuberculosis be put on ART for life-not a cost-effective approach especially in resource-constrained settings. This point is highlighted by our finding that over 7% of HIV-positive individuals with tuberculosis had CD4 counts greater than 200 cells/μL, indicating that it was not compelling to otherwise start ART in them. It is therefore imperative that tuberculosis should be reclassified from a category C to category B condition or that at least, tuberculosis should not be considered grounds for initiation of ART in the absence of corroborative low CD4 counts, in countries with high prevalence of tuberculosis.

This study shows that the presence of accompanying evidence of immunosuppression in the form of category B and C conditions in the HIV-positive patients with active tuberculosis is associated with significantly lower CD4 count; counter-intuitively, severe forms of tuberculosis are not necessarily associated with lower CD4 counts. This finding

Table 3
CD4 counts across patients according to severity and form of tuberculosis.

Patient	Form of tuberculosis	Number of patients	Patient percentage (%)	CD4 count
Mild tuberculosis	Pulmonary parenchymal tuberculosis	39	27.9	84.5±85.0
	Tubercular lymphadenitis	35	25.0	91.4±87.7
	Tubercular effusion	7	5.0	108.7±103.4
	Tubercular peritonitis	3	2.1	77.3±18.0
Severe tuberculosis	Disseminated tuberculosis	39	27.9	84.5±79.4
	Tubercular meningitis	8	5.7	77.6±65.2
	Tuberculoma	5	3.6	59.4±38.9
	Miliary tuberculosis	3	2.1	115.7±50.7
	Tubercular pericarditis	1	0.7	7.0

Table 4
Comparison of baseline characteristics and CD4 counts across patients with different severity of tuberculosis

Tuberculosis	Age (years)	Male-to-female ratio	CD4 count (cells/μL)
Mild tuberculosis (n=84)	40.1±9.2	68:16	89.1±85.3
Severe tuberculosis (n=56)	39.8±7.7	41:15	81.6±72.9

emphasizes the need to carefully search for such co-existing conditions in these patients, and not to simply focus on the form of tuberculosis. Certainly, patients with concomitant category B and C conditions are likely to have a more advanced infection with HIV and therefore have poorer long-term outcomes, even when compared to patients with severe tuberculosis without such conditions. Incorporating such an approach at the time of dealing with HIV-tuberculosis co-infected patients would grant the treating physician a better perspective of the degree of immunosuppression and correspondingly the need for initiation of ART.

Conflict of interest statement

We declare that we have no conflict of interest.

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