Research Paper Medicine

CORELATION OF CD4 COUNT WITH THE CLINICO-RADIOLOGICAL AND MICROBIOLOGICAL PROFILE IN PATIENTS WITH HIV AND PULMONARY TUBERCULOSIS COINFECTION

Dr. Sivaresmi Unnithan MD Associate Consultant, Department of Pulmonary Medicine. Calcutta Medical Research Institute.

Dr. P. D. Motiani MD Ex- Head of the Department, Department of T.B & Respiratory Diseases. Kamla Nehru Chest Hospital, Jodhpur

KEYWORDS

Introduction:
Currently, about 33 million people are HIV-infected, and almost one-third are also infected with TB.[1,2] It is an established fact that tuberculosis is one of the commonest opportunistic infections in patients with HIV infection and can develop at any stage of the disease.[3] In fact, the risk of developing TB in HIV infected patients has been estimated to be 5 – 15%/year (5 – 10% during life time of non HIV-1 infected patients).[4] Again, during the course of tuberculosis, the HIV virus burden and heterogeneity increases.[5,6]

The occurrence of TB does not correlate with CD4 counts, although TB is more commonly seen in severely immuno-compromised patients.[7] HIV induced immunosuppression affects the clinical presentation of TB and it is also noted that in those with CD4 counts of ≤200, there were 6.0% of patients with drug resistance TB.[7] Among the various factors related to TB drug resistance severe immunodeficiency plays an important role.[7]

Cavitating lesions are rarely seen in patients with a CD4 counts < 200/mm [8,9] instead atypical features like lower lobe involvement with diffuse infection are seen more commonly.

Although Mantoux test positivity for TB diagnosis depends on the immune status of an individual, several studies have shown that Mantoux test is not helpful to diagnose TB in those with late HIV disease [8,10].

Aims & Objectives:
To determine what influence the CD4 cell count has on the tuberculin skin sensitivity, the appearance of the chest radiograph, on the likelihood of positive acid-fast smears, presence of drug resistance, and on the presence of disseminated infection in patients with HIV and pulmonary tuberculosis coinfection.

Method & Materials:
The present study is a prospective observational one which was done on 84 HIV positive patients microbiologically radiologically and clinically diagnosed with Pulmonary Tuberculosis in Dr. S. N. Medical College, Jodhpur. Their sputum samples were sent to the IRL [Kamla Nehru State TB Demonstration & Training Centre, Jawaharlal Nehru Medical College] in Ajmer for mycobacterial culture and later Drug Sensitivity testing for four ATT drugs- H, R, S and E.

Those HIV seropositive patients of all ages [confirmed at the Voluntary Counseling and Testing Center (VCTC), Department of Microbiology, Dr. S.N.Medical College, using three different methods (ELISA / rapid tests / simple tests) as per National AIDS Control Organization (NACO) guidelines][11] were included in the study who were either microbiologically proved Sputum positive for AFB. [Sputum smears for acid fast bacilli [AFB] was examined at our DOTS centre, Kamla Nehru Chest Hospital.] or whose Sputum was negative for AFB but their clinical symptoms and Chest radiography is highly suggestive of Pulmonary Tuberculosis. Both fresh and re-treatment cases of Pulmonary TB were included. All clinical stages of HIV infection according to the WHO classification were included.

Patients suffering from other immunosuppressive conditions like Diabetes Mellitus, Primary immune deficiencies, Extra pulmonary TB or on long term steroids/ immunosuppressive drugs were excluded from the study.

CD4 cell immune-phenotyping was performed using a BD FACS count system [12]

Results:

The study population consists of predominantly males [60/84], most of them [43/60] in the age group of 31-40 years.

Most of the study population presented with CD4 counts less than 200/cumm [~81%], among whom the maximum presentation were with CD4 counts <50/cumm. (Table 1) The mean CD4 count was 116 [Range = 8-440].

Table 1:CD4 count at the time of presentation

	<50	51-100	101-200	>201	TOTAL
MALE	22	11	16	11	
FEMALE	10	5	4	5	
TOTAL	32	16	20	16	84
PERCENTAGE	38.09%	19.05%	23.81%	19.05%	100%

16.67% [3/18] of the 18 sputum negative cases had CD4 counts >201/ cumm whereas only 19.7 % of the 66 sputum positive cases in the study had CD4 counts >201/cumm. Again, 75% of the 32 cases with CD4 counts <50/cumm were sputum positive, the rest 25% were sputum negative (Table 2).

Table 2:Association of CD4 count with sputum positivity

		<50	51-100	101-200	>201	TOTAL
SP +ve	NO. OF CASES	24	11	18	13	66
	%age	28.57%	13.1%	21.43%	15.48%	78.57%
SP -ve	NO. OF CASES	8	5	2	3	18
	%age	9.52%	5.95%	2.38%	3.57%	21.43%

89.47% [35/38] of the patients with disease of only <6mns duration had CD4 count <200/cumm at the time

of presentation. [Table3] None of the patients with CD4 count less than 100/cumm presented in WHO clinical stages 1. [Table 4] Those with CD4 counts <50 mostly showed up with WHO clinical stages 3 and 4 [24/32]. It is important to note that the WHO clinical staging was done when the patients presented to us the first time, before they were diagnosed with tuberculosis. After diagnosis of TB, the patients were automatically grouped in Stage 3, but by then the data was already taken for the present study.

Table 3:CD4 count with disease duration at the time of presentation

	<50		51-100		101-200		>201		Total
	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage	
<6mn	15	17.77%	11	13.1 %	9	10.71%	3	3.57%	38
6mn-1yr	5	5.95%	2	2.38 %	0	0	0	0	7
>1yr	12	14.29%	3	3.53 %	11	13.1%	13	15.48%	39
Total	32		16		20		16		84

Table 4:Association of CD4 count with WHO Clinical staging

	<50		51-100		101-200		>201		TOTAL	% AGE
	NO. OF CASES	% AGE	NO. OF CASES	% AGE	NO. OF CASES	% AGE	NO. OF CASES	% AGE		
I	0		0		5		0		5	
		0		0		5.95 %		0		5.95 %
II	8		7		10		7		32	
		9.52 %		8.33 %		11.90 %		8.33 %		38.09 %
III	17		5		5		7		34	
		20.24 %		5.95 %		5.95 %		8.33 %		40.48 %
IV	7		4		0		2		13	
		8.33%		4.76 %		0		2.38 %		15.48 %
TOTAL									84	100%

75% of the study population showed Mantoux test [Tuberculin skin sensitivity] to be negative. 47.61% showed no reaction to Tuberculin at all [Tuberculin anergy]. Of them 85% [34/40] were those with CD4 count <200/cumm. 71.88% [23/32] with CD4 count <50/cumm had tuberculin anergy.[Table 5]

Table 5:Association of CD4 count with Mantoux test

		<50	51-100	101-200	>201	TOTAL
MT non reactive	NO. OF CASES	23	9	2	6	40
	%age	27.38%	10.71%	2.38%	7.14%	
MT <5mm	NO. OF CASES	7	5	8	3	23
	%age	8.33%	5.95%	9.52%	3.57%	
MT >=5mm	NO. OF CASES	2	2	10	7	21
	%age	2.38%	2.38%	11.91%	8.33%	

88.89% [8/9] cases of Far advanced Pulmonary TB [according to the NTA of USA classification of Chest Radiography] have CD4 counts <200/cumm. (Table 6).

Of the patients with 68 patients with CD4 counts less than 200/cumm, 57.35% [31+8] were those whose Chest X-ray shows moderately and far advanced disease. There were only 3 patients with CD4 counts >350/cumm and all of them have shown Chest X-ray features of minimally advanced disease.

Table 6:Chest radiograph classification of disease extent in Pulmonary TB [National tuberculosis Association of the USA]

	<200	201-350	>351	Total	%age
Minimal	29	10	3	42	50%
Moderately advanced	31	2	0	33	39.29%
Far advanced	8	1	0	9	10.71%

Among these 28/84 patients, 24 patients [20.16%] with atypical presentation in their Chest X-ray were with CD4 count<200/cumm. Out of the 68 patients with CD4 count<200/cumm, 10.71% have Miliary/ disseminated TB disease. In fact, one patient had Ground Glass Opacity in her CXR and her CD4 count was only 31. Only 8.33 % have typical cavitating lesions in their chest radiograph.

41/84 patients' sputum samples were noted leaked or contaminated before being subjected for culture & sensitivity and therefore, only 43 culture reports were available. Of the 43 cases, we found that among those whose culture was MDR and mono resistant[13 cases], 9 [9/13=69.23%] were those with CD4 count <200/cumm. Among the 12 MDR patients, the mean CD4 count was only 86.4/cumm in the fresh cases and 134.14/cumm in the retreatment cases. In fact, 41.67% [5/12] of these MDR have CD4 counts <50/cumm only (Table 7). The percentage of drug resistance among patients with <200/cumm CD4 count was 26.47% [9/34].

Table 7: Association of CD4 count with sputum culture [43 cases]

		<50	51-100	101-200	>201	TOTAL
Culture SENSITIVE	NO. OF CASES	6	3	7	2	18
	%age	12%	6%	14%	4%	
Culture RESISTANT	NO. OF CASES	5	2	1	4	12
	%age	10%	4%	2%	8%	
Culture NEGATIVE	NO. OF CASES	4	3	2	3	12
	%age	8%	6%	4%	6%	
MONORESIS	NO. OF CASES	1	0	0	0	1
	%age	2%	0	0	0	

Discussion:

In the present study, most of the study population presented with CD4 counts less than 200/cumm [~81%] A survey from London hospitals on 188 patients in 1999 has shown that patients who are diagnosed with both HIV and tuberculosis (TB) are among the most difficult group to treat and their average CD4 count was 94. Curvo-Semedo et al., 2005 found the average CD4+ T-cell count in HIV-positive individuals in their study was 95.38 ± 62.8 cells/mm3, indicating that patients had a very compromised immunity.[13,14]

Likewise, it has been observed in the present study, with mean CD4 count being just 116/cumm, there is definitely compromised immunity which predisposed to the development of Pulmonary TB which is so prevalent in developing countries like India. Most of the patients who were known cases of HIV [39/84] developed TB [34/39] when their CD4 count went below 200/cumm. Maximum number of these known HIV cases [28%] presented with CD4 counts <50/cumm. There seems to be no particular trend in the present study in any increasing positivity of sputum as the CD4 count rises(Table 2). Robert L. Smith et al also found that for patients with HIV, the likelihood of a positive smear was independent of CD4 cell counts

and drug resistance. Patients with HIV and CD4 count <50, 50 to 200, and >200 had positive acid-fast smear rates of 58 percent, 60 percent, and 56 percent, respectively; HIV infected patients with drug-resistant organisms had 65 percent positive smears.[15] The expectation that infection with HIV would reduce the sensitivity of acid-fast smears, due to a decreased frequency of cavitary pulmonary MTB, has not been substantiated.[15]

Most of the patients with disease of only <6mns duration had CD4 count <200/cumm at the time of presentation.[Table3] Therefore, one could predict progression within a patient of CD4 count <200/cumm within 6 months of the disease. COBO J et al in Spain in 2001 conducted a study on a total of 266 patients. Twenty (7.5%) patients developed MDRTB and 16 (80%) of these were diagnosed within 10 months of exposure.[16] The present study showed the mean of 16.42 months of disease duration before they were diagnosed with the co-infection.

Col MPS Sawhney et al in 2006 noted that HIV infected cases associated with tuberculosis with induration on TST had average CD4 counts of 129.5 as compared to 246.3/cmm in those without tuberculosis. The average CD4+ lymphocyte count was found to be significantly lower in cases with nil TST results than with = or >10mm. In India where both these diseases are endemic, tuberculosis may develop during early HIV infection, while the body's immunity is still largely unimpaired and TST shows = or >10mm results in almost 45% of their cases. In another 45% with TST of 0-4mm, the CD4+ lymphocyte count is likely to be lower than 200/cmm. Hence they recommend that all cases with TST of = or >10mm and cases with nil induration with CD4+ count of <200/cmm should be considered as high-risk for developing tuberculosis.[17]

The same was found in the present study i.e ~64%[54/84] of the study population was seen to be MT negative but with either microscopically or culture proved Pulmonary Tuberculosis and all of them had CD4 counts <200/cumm. It clearly shows the decreased Type IV Hypersensitivity associated with HIV and TB as a coinfection.

Of the patients with 68 patients with CD4 counts less than 200/cumm, 57.35% [31+8] were those whose Chest X-ray shows moderately and far advanced disease. Studies have shown the following presentations on chest X-rays: findings consistent with progressive primary TB; findings consistent with postprimary TB; miliary TB; minimum alterations in up to 5% of the cases; and normal chest X-rays in up to 14% of the cases.[18,19]

Only 8.33 % have typical cavitating lesions in their chest radiograph. This conforms to the finding by Dawson P et al, that while patients with higher CD4 cells (>350 cells/mm3) have radiographic abnormalities similar to their HIV negative counterparts, patients with immunosuppression often have minimal or atypical findings.[20]

Studies have shown that the post-primary form is more common in patients with CD4 > 200 cells/mm3. More severe immunosuppression makes it more likely that chest X-ray presentations will be atypical and that there will be greater extrapulmonary involvement, as well as increasing the risk of mycobacteremia.[19]

Of the 43 cases with culture reports, it was found that among those whose culture was MDR and mono resistant[13 cases], 9 [9/13=69.23%]were those with CD4 count <200/cumm. COBO J et al in Spain in 2001 found that severe immunosuppression independently increases the risk of development of MDRTB after exposure in the context of a nosocomial outbreak. CD4 count at the time of exposure (Te-CD4) < 100/micro-L was significantly associated with MDRTB development by Kaplan Meier analysis.[16] In the present study, there were 26.47% drug resistance TB in those with CD4 counts of ≤200 compared to C K Ong et al in 2008 where they found 6.0% with drug resistance TB.[7]

Conclusion:

The more immunocompromised the patients are [CD-4count<200], more are the chances of acquiring tuberculosis which results in presentation in late WHO clinical stages. The chances of advanced disease and atypical presentation on the chest radiograph are also more with CD4count<200. There is in fact, more probability of Mantoux negativity and drug resistance [MDR TB] with decreasing CD4 count. No particular trend of sputum positivity with CD4 count was noted in this study. Therefore, in severely immuno-compromised HIV patients, we need to have a high index of suspicion especially to diagnose TB [especially drug resistance TB] in countries with high tuberculosis rates.

REFERENCES

1. Chavez Pachas AM, Blank R, Smith Fawzi MC, Bayona J, Becerra MC, Mitnick CD. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. Int J Tuberc Lung Dis 2004;8:52-8. | 2. MULTIDRUG AND EXTENSIVELY DRUG-RESISTANT TB (M/XDR-TB): 2010 GLOBAL REPORT ON SURVEILLANCE AND RESPONSE | 3. Manifestations of tuberculosis in HIV/AIDS patients and its relationship with CD4 count. HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/?term=Jaryal%20A%5Bauth%5D"Ajay Jaryal, HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/?term=Raina%20R%5Bauth%5D"Rajeev Raina, HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/?term=Sarkar%20M%5Bauth%5D"Malay Sarkar,1 and HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/?term=Sharma%20A%5Bauth%5D"Ashok Sharma. Lung India. 2011 Oct-Dec; 28(4): 263–266. | 4. Raviglione M, Harries A, Msika R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS 1997; 11(suppl B): S115-S123. | 5. Toossi Z. Virological and immunological impact of tuberculosis on human immuno-deficiency virus type 1 disease. Journal of infectious diseases, 2003, 188(8):1146–55. | 6. Clinical and laboratory profile of patients with tuberculosis/HIV coinfection at a national referral centre: a case series. P. Tabarsi, S.M. Mirsaeidi, M. Amiri, S.D. Mansouri, M.R. Masjedi and A.A. Velayati. Eastern Mediterranean Health Journal, Vol. 14, No. 2, 2008 | 7. Tuberculosis-HIV Coinfection: The Relationship Between Manifestation Of Tuberculosis And The Degree Of Immunosuppression (CD4 Counts) C K Ong, W C Tan, K N Leong, A R Muttalif. IeJSME 2008: 2 (2): 17-22 | 8. Rieder HL, Cauthen GM, Comstock GW & Snider DE (1989). Epidemiology of tuberculosis in the United States. Epidemiologic Reviews 11, 79-98. | 9. 10. Smith RL, Yew K, Berkowitz KA, Aranda CP Factors affecting the yield of acid fast sputum smears in patients with HIV and tuberculosis. Chest 1994; 106: 684-6. | 10. Jones BE, Young SMM, Antoniskis D, Davidson PT, Kramer F et al. Relationship of the manifestation of tuberculosis to CD4 counts in patient with human immunodeficiency virus infection. Am. Rev. Respir. Dis. 1993; 148: 1292-7. | 11. www.nacoonline.org/publication: HIV-TB Co-infection: A Guide for Medical Officers (2004). | 12. Department of AIDS Control Ministry of Health & Family Welfare;Annual Report 2009 --10 http://www.nacoonline.org/upload/AR%20200910/NACO_AR_English%20corrected.pdf | 13. Curvo-Semedo L, Teixeira L, Caseiro-Alves F (2005). Tuberculosis of the chest. Eur. J. Radiol. 55:158-172. | 14. Sputum cellularity in pulmonary tuberculosis: A comparative study between HIV-positive and –negative individuals Rosemeri Maurici da Silva, Paula Stocco, Maria Luiza Bazzo and Mariana Chagas http://www.academicjournals.org/jahr/PDF/Pdf2010/Feb/Maurici%20da%20Silva%20et%20al.pdf | 15. Factors Affecting the Yield of Acid-fast Sputum Smears in Patients With HIV and Tuberculosis Robert L. Smith, Kenneth Yew, Kenneth A. Berkowitz and Conrado P. Aranda Chest 1994;106;684-686 | 16. Impact of CD4 Count at the Time of Exposure to Multi-Drug Resistant Tuberculosis (MDRTB) in the Risk of Developing MDRTB among HIV-Infected Subjects. Cobo J, Moreno L, Abraira V, Guerrero A, Muriel A, Navas E, Asensio A, Gomez-Mampaso E, Moreno S; Interscience Conference on Antimicrobial Agents and Chemotherapy Abstr Intersci Conf Antimicrob Agents Chemother Intersci Conf Antimicrob Agents Chemother. 2001 Dec 16-19; 41: abstract no. I-246. | 17. Significance of Tuberculin Testing in HIV Infection: An Indian Perspective Col MPS Sawhney*, Maj Gen YK Sharma MJAFI, Vol. 62, No. 2, 2006 | 18. Leung AN. Pulmonary TB: the essentials. Radiology 1999;210:307-22. | 19. Tuberculosis/HIV co-infection Co-infecção tuberculose/HIV Antônio Carlos Moreira Lemos J Bras Pneumol. 2008;34(10):753-755 | 20. Chest radiograph reading and recording system: evaluation for tuberculosis screening in patients with advanced HIV R. Dawson,P. Masuka,D. J. Edwards,E. D. Bateman,L-G. Bekker, R. Wood,S. D. Lawn Int J Tuberc Lung Dis 14(1):52–58 2010 The Union. |