Significance of Tuberculin Testing in HIV Infection: An Indian Perspective

Col MPS Sawhney*, Maj Gen YK Sharma[†]

Abstract

Background: Tuberculin skin testing (TST) is a reliable tool in the diagnosis of tuberculous infection and is important in its control. However, it may be false negative in immunocompromised patients like HIV-infected.

Method: We examined the pattern of TST results in 523 newly diagnosed HIV-positive patients. CD4, CD8 and absolute lymphocyte counts were done by flowcytometry in 63 of these cases.

Results: 56 (44.10%), 15 (11.81%) and 56 (44.10%) of the 127 cases with tuberculosis and 293 (73.99%), 41 (10.35%) and 62 (15.66%) of the 396 cases without any clinical evidence of tuberculosis showed TST results of 0-4, 5-9 and $\geq$ or $>$ 10 mm respectively. Significantly more ($P<0.05$) number of cases with TST of $\geq$ or $>$ 10mm and significantly lesser ($P<0.05$) number of cases with TST of 0-4 mm are likely to develop tuberculosis. The average CD4+lymphocyte count was found to be significantly lower in cases with nil TST results than with $\geq$ or $>$ 10mm. 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.

Conclusion: 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 $\geq$ or $>$ 10mm results in almost 45% of our cases. In another 45% with TST of 0-4mm, the CD4+ lymphocyte count is likely to be lower than 200/cmm. In those with nil induration, TST of 5-9 mm cannot be taken as an independent marker for suspecting tuberculosis in the HIV infected. Hence we recommend that all cases with TST of $\geq$ or $>$ 10mm and cases with nil induration with CD4+ count of $<$ 200/cmm should be considered as high-risk for developing tuberculosis.

MJAFI 2006; 62 : 104-107

Key Words: Tuberculin skin test; HIV infection

Introduction

HIV positive cases are grouped into three categories as per the new CDC case definition of 1993 [1], which added three new AIDS-defining illnesses viz. *Mycobacterium tuberculosis* infection, recurrent bacterial pneumonia and cervical carcinoma. While in United States, *Pneumocystis carinii* is the commonest opportunistic infection (OI) and only 10% of AIDS patient have mycobacterial disease [2], studies from India reported clinical tuberculosis in almost 50% of the patients of AIDS [3,4]. Among the first 243 HIV-positive cases registered in our centre between Jan 1990 to Apr 1994, tuberculosis was detected in only 15 (6.2%) [5]. However, 176 (28.76%) of the 612 cases registered between Jan 1997 to Aug 2002, presented with mycobacterial disease [6]. This highlights that those diagnosed with HIV infection need to be kept under surveillance and be given prophylactic treatment for tuberculosis at an appropriate time. CDC recommends that HIV-positives with tuberculin test reaction of 5mm or more are at greater risk of developing tuberculosis

and hence they should be administered prophylactic treatment [7]. There is a need to lay down guidelines for prophylactic treatment of HIV-positives in the Indian setting where a large part of the population is likely to be TST positive having received BCG vaccination in the childhood.

Material and Methods

Records of 612 newly diagnosed cases of HIV infection in serving Armed Forces personnel registered at Command Hospital (Southern Command), Pune between Jan 1997 to Aug 2002 were analysed. Tuberculin skin test (TST) by Mantoux method was carried out in 523 of them. 2-Colour EPICS-XL Coulter flowcytometry was used for CD4, CD8 and absolute lymphocyte (ALC) counts in 63 of these cases. Normal reference values of CD4 and CD8 by this method were 500-2000 and 350-1750/cmm respectively. For the purpose of correlation with tuberculosis the patients were divided into three groups of 0-4mm, 5-9mm and $\geq$ or $>$ 10mm. For the purpose of study of CD4/CD8 counts, the patients were divided into four categories i.e. nil (total anergy), 1-4, 5-9 and 10mm or more of induration.

*Senior Advisor (Derm & Ven), Base Hosp, Delhi Cantt. [†]Commandant, Command Hospital, Northern Command, C/o 56 APO.

Results

Only two out of the 523 patients were females as Armed Forces are male predominant. Average age of the patients was 33.82 years (range 19-57). Age of the patients and TST results are shown in Table 1.

Results of TST in HIV-patients with and without tuberculosis are shown in Table 2. Significantly larger number of patients without tuberculosis had induration of 0-4mm (SE 5.09, CI 95%, $P < 0.05$). Similarly, significantly larger number of HIV-positive cases with induration of $\geq$ or > 10 mm had tuberculosis (SE 4.77, CI 95%, $P < 0.05$). There was no significant difference in proportion of cases with or without tuberculosis in those with TST results of 5-9mm (SE 3.26, CI

95%, $P > 0.05$).

The comparison of TST with CD4, CD8, ALC and CD4% is shown in Table 3. CD4 count was significantly lower in patients with nil TST reaction than in patients with reaction of 10mm or more (SE 42.05, $P < 0.05$), however it was not found significantly lower than in patients with reaction of 5-9mm (SE 48.84, $P > 0.05$).

TST and average CD4 counts/cmm in cases with only tuberculosis, those tuberculosis with a category B condition, those with a category B condition without tuberculosis and those with neither tuberculosis nor with any category B condition are shown in Table 4. The category B conditions in cases with tuberculosis were herpes zoster (HZ) in 3 and oral candidiasis in 4 and in those without TB, bacillary angiomatosis and oral candidiasis in one, only oral candidiasis in 10 and HZ in 15. It is seen that average CD4 count in six cases of tuberculosis with nil induration were less than 200/cmm, while it was more than 200/cmm in cases, which neither had tuberculosis nor any associated category B condition. However, it was less than 200/cmm in those cases which had an associated category B condition.

Table 1

Age and tuberculin test in HIV-positive patients

Age	Tuberculin test			Total
	0-4 mm No. (%)	5-9 mm No. (%)	≥ 10 mm No. (%)	
0-10	0	0	0	0
11-20	2 (100)	0	0	2 (0.38)
21-30	122 (65.59)	22 (11.83)	42 (22.85)	186 (35.56)
31-40	183 (68.03)	28 (10.41)	58 (21.56)	269 (51.43)
41-50	33 (63.46)	4 (7.69)	15 (28.85)	52 (9.94)
51-60	9 (64.29)	2 (14.29)	3 (21.43)	14 (2.68)
Total	349 (66.73)	56 (10.71)	118 (22.56)	523 (100)

Table 2

Tuberculin test in HIV positives with and without tuberculosis

Tuberculin test (mm)	No. (%)	With tuberculosis						Without TB (%)
		Pulm (%)	Gland (%)	Abd (%)	Dis (%)	Others (%)	Total (%)	
0-4	349 (66.73)	33 (40.74)	3 (60)	1 (100)	17 (47.22)	2 (50.00)	56 (44.10)	293 (73.99)
5-9	56 (10.71)	10 (12.34)	0	0	5 (13.89)	0	15 (11.81)	41 (10.35)
≥ 10	118 (22.56)	38 (46.91)	2 (40)	0	14 (38.89)	2 (50.00)	56 (44.10)	62 (15.66)
Total	523	81	5	1	36	4	127	396

Pulm-pulmonary, abd-abdominal, dis-Disseminated, Others-TBM-2, Spine-1, pericarditis-1

Table 3

Tuberculin test and average CD4, CD8, ALC, CD4 : CD8 and CD4% in HIV positive patients

Tuberculin test (mm)	No	CD4/Cmm (SD)	CD8/cmm	ALC/cmm	CD4:CD8	CD4%
0	41	229.07 (167.21)	955.20	1951.80	0.24	11.74
1-4	2	409.50 (222.74)	1004.50	2100.00	0.41	19.50
5-9	8	264.50 (116.74)	854.88	1875.00	0.31	14.11
≥ 10	12	317.50 (114.22)	1003.42	2291.67	0.32	13.85
Total	63	256.10	955.10	2012.00	0.27	12.73

Table 4

Tuberculin test and average copy counts/cmm in those with and without tuberculosis associated with or without category B conditions

Tuberculin test (mm)	With tuberculosis			Without tuberculosis		
	Only TB	With associated Cat B condition	Total	With Cat B condition	Without Cat B condition	Total
	(No.)	(No.)	(No.)	(No.)	(No.)	(No.)
0	134 (2)	127.25 (4)	129.5 (6)	193.5 (20)	316.7 (15)	246.3 (35)
1-4	-	-	-	252 (1)	567 (1)	409.5 (2)
5-9	215 (2)	-	215 (2)	205 (3)	357 (3)	281 (6)
≥ 10	294 (2)	155 (3)	210.6 (5)	465 (2)	365.4 (5)	393.86 (7)
Total	214.50 (6)	139.14 (7)	173.84 (13)	217.96 (26)	342.29 (24)	277.64 (50)

persons taking immunosuppressive drugs (eg. corticosteroids), severely malnourished and the elderly. Nevertheless it is still useful in detecting infection in those who are in close contact of patients with tuberculous disease. Once a skin test is found to be reactive, further diagnostic studies should be done to rule out tuberculous disease. Once ruled out, preventive therapy with isoniazid or a combination of drugs should be instituted. TB cannot be eliminated until the importance of preventive therapy is recognized by all [7].

Some interesting findings have come to light in this study. A significantly larger number of HIV positive cases with tuberculin test result of 10mm or more are likely to have tuberculosis in the Indian setting as is the case with HIV-seronegatives. The same has not been proved true with reaction of 5-9mm. Hence, in countries endemic for tuberculosis, the infection is likely to occur early, when the body immunity is still intact, giving rise to a strongly positive tuberculin reaction. CDC recommended that tuberculin reaction of 5mm or more should be considered as positive in HIV-positive cases [8]. Graham et al went even further and recommended that TST definition of 2mm or more would appear to be a better cutoff in HIV-infected [9]. This may not be true for Indian settings and other countries where tuberculosis is endemic and the diseases develops due to reactivation of the existing focus.

In advanced HIV disease, when there is increased immunosuppression, the body may not be able to produce adequate TST results [10]. Janis et al believed that tuberculin testing and anergy testing with other antigens like candida, trichophyton, tetanus toxoid, proteus, diphtheria, etc should be done in all HIV cases and those who are anergic to both are at greater risk of developing tuberculosis [11]. On the other hand some authors have

concluded that TST has a limited value in populations with high seropositivity for HIV [12-14]. In the present study we have seen that equal number of patients (44.10%) of tuberculosis had tuberculin test reaction of 0-4mm as compared to those with TST of 10mm or more. How then to identify, high-risk amongst this group? It was seen that cases of tuberculosis with nil induration have CD4 counts below 200/cmm, in contrast to patients who neither have tuberculosis nor an associated category B condition. This suggests that all HIV cases without clinical evidence of tuberculosis with TST positivity of 10mm or more and all cases of negative reaction to TST who have CD4 counts lower than 200/cmm are at risk of developing tuberculosis and should be administered chemoprophylaxis. Madhi et al, however felt that TST is of limited value as an adjunct in diagnosing tuberculosis in HIV-infected children. CD4+ lymphocyte counts and concurrent DTH testing are not useful for predicting tuberculin reactivity in HIV-infected patients with tuberculosis [15]. Diaghoug et al also felt that there is no correlation between CD4+ cell count and TST results and both should be independent markers of immunosuppression [16]. This is contrary to our findings. Chemoprophylaxis in this high risk group is associated with marked reduction in tuberculosis risk [17, 18]. Some authors however do not conform to this view [19].

To conclude, in countries like India where both the diseases are endemic, tuberculosis may develop early in the HIV disease, when the body's immunity is still largely unimpaired and TST showed = or > 10mm results in almost 45% of such cases. In another 45% with TST 0-4mm, the CD4+ lymphocyte count is likely to be lower than 200/cmm in those with nil induration. TST of 5-9 mm has not been found to be an independent marker for developing tuberculosis in the HIV infected. Hence

we recommend that all cases with TST of $\geq$ or $>$ 10 mm and cases with nil induration with CD4+ count of $<200/\text{cmm}$ should be considered as high-risk for developing tuberculosis and should be administered chemoprophylaxis.

Conflicts of Interest

None identified

References

- Center for Disease Control. 1993 Revised classification system for HIV infection and expanded surveillance of definition for AIDS among adolescent and adults. *MMWR* 1992; 41(rr-17): 1-19.
- Reider HL, Cauthen GM, Kelly GD, Block AB, Snider DE Jr. Tuberculosis in the United States. *JAMA* 1989; 262: 385-9.
- Kaur A, Babu PG, Jacob M, Narasimhan C, Ganesh A, Saraswathi NK et al. Clinical and laboratory profile of AIDS in India. *J Acquir Immune Defic Syndr* 1992;5 :883-9.
- Kumaraswamy N, Solomon S, Flanagan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural History of Human Immunodeficiency Virus Disease in Southern India. *Clin Infect Dis* 2003; 36: 79-85.
- Jayaswal R, Arora PN, Panda BN. HIV in tuberculosis. *MJAFI* 1995; 51: 259-63.
- Sawhney MPS, Sharma YK, Sayal SK. Mode of detection of HIV infection-a retrospective study in 612 cases. Accepted for publication in *MJAFI*.
- Hanson CA, Reichman LB. Tuberculosis skin testing and preventive therapy. *Semin Respir Infect* 1989; 4: 82-8.
- Klein RS, Gourevitch MN, Teetor R, Schoenbaum EE. The incidence of tuberculosis in drug users with small tuberculin reaction sizes. *Int J Tuberc Lung Dis* 2001; 5: 707-11.
- Graham NM, Nelson KE, Solomon L, Bonds M, Rizzo RT, Scavotto J, Astemorski J, Vjabov D. Prevalence of tuberculin positivity and skin test anergy in HIV-1-seropositive and seronegative intravenous drug users. *JAMA* 1992; 267: 369-73.
- Portu JJ, Aldamiz-Etxebarria M, Agud JM, Almaraz MJ, Ayensa C. Tuberculin skin testing in intravenous drug users: differences between HIV-seropositive and HIV-seronegative subjects. *Addict Biol* 2002; 7 : 235-41.
- Janis EM, Allen DW, Glesby MJ, Carey LA, Mundy LM, Gopalan R, et al. Tuberculin skin test reactivity, anergy, and HIV infection in hospitalized patients. *Am J Med* 1996; 100: 186-92.
- Slovic BS, Plitman JD, Haas DW. The case against anergy testing as a routine adjunct to tuberculin skin testing. *JAMA* 2000; 283: 2003-7.
- Yanai H, Uthairoravit W, Mastro TD, Limpakarnjanarat K, Sawanpanyalert P, Morrow RH Jr, et al. Utility of tuberculin and anergy skin testing in predicting tuberculosis infection in human immunodeficiency virus-infected persons in Thailand. *Int J Tuberc Lung Dis* 1997; 1: 427-34.
- Duncan LE, Elliot AM, Hayes RJ, Hira SK, Tembo G, Mumba GE, et al. Tuberculin sensitivity and HIV-1 status of patients attending a sexually transmitted diseases clinic in Lusaka, Zambia: a cross-sectional study. *Trans R Soc Trop Med Hyg* 1995; 89: 37-40.
- Madhi SA, Gray GE, Huebner RE, Sherman G, Mc Kinnon D, Pettifor JM. Correlation between CD4+ lymphocyte counts, concurrent antigen skin test and tuberculin skin test reactivity in human immunodeficiency virus type 1-infected and uninfected children with tuberculosis. *Pediatr Infect Dis J* 1999; 18: 800-5.
- Diagbougba S, Fumoux F, Ledru E, Sanou PT, Barro D, Marchal G. Lack of direct correlation between CD4 T-lymphocyte counts and induration sizes of the tuberculin skin test in human immunodeficiency virus type 1 seropositive patients. *Int J Tuberc Lung Dis* 1998; 2:317-23.
- Gourevitch MN, Hartel D, Selwyn PA, Schoenbaum EE, Klein RS. Effectiveness of isoniazid chemoprophylaxis for HIV-infected drug users at high risk for active tuberculosis. *AIDS* 1999; 13: 2069-74.
- Bucher HC, Griffith LE, Guyatt GH, Sudre P, Naef M, Sendi P, et al. Isoniazid prophylaxis for tuberculosis in HIV infection : a meta-analysis of randomized controlled trials. *AIDS* 1999; 13: 501-7.
- Hawken MP, Meme HK, Elliot LC, Chakaya JM, Morris JS, Githui WA, et al. Isoniazid preventive therapy for tuberculosis in HIV-1- infected adults : results of a randomized controlled trial. *AIDS* 1997; 11: 875-82.