CORRELATION OF RADIOGRAPHIC PATTERNS OF PULMONARY TUBERCULOSIS WITH CD4+ CELL COUNTS AMONG PATIENTS WITH HIV/AIDS IN MAIDUGURI, NIGERIA

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Abstract

Background: Tuberculosis remains an important infection in patients with human immunodeficiency virus (HIV) infection. It may develop at any stage of HIV infection, but most patients have been shown to have CD4+ counts of between 200 and 500/µl. Patients with higher CD4+ counts often present in "classic" fashion (upper zone infiltrates ± cavities) whereas those with low CD4+ counts are more likely to present atypically. The chest radiographic appearances of HIV-seropositive patients presenting with pulmonary tuberculosis (PTB) are diverse, creating difficulty in diagnosis and treatment. While some studies reported correlation between CD4+ cell counts and radiographic patterns, others have failed to demonstrate that

Objectives: The aims of this study was to determine the relationship between CD4+ cell counts and the various radiographic patterns of pulmonary tuberculosis in HIV-infected patients.

Methods: Sixty consecutive confirmed HIV-seropositive patients with newly diagnosed sputum smear positive pulmonary tuberculosis were enrolled from September 2001 to August 2002. Anteroposterior chest x-rays were evaluated for the presence of apical opacities with or without cavitation (typical) or miliary, lower or mid-zone and reticulonodular opacities, pleural effusion, hilar adenopathy and normal radiograph (atypical).

Results: The age range of the patients was 18-55 years (Mean ± SD: 33.9 ± 8.42) and they comprised of 34 males and 26 females.

All those with CD4+ cell counts <200 cells/µl (43%) had atypical pattern whereas typical was seen only in those with CD4+ counts ≥200 cells/µl ($p<0.01$). Nine of 34 patients (26%) with CD4+ counts 200 cells/µl had typical pattern. The mean CD4+ cell counts of those with typical versus atypical pattern were 442.2 ± 89.2 cells/µl and 202.2 ± 76.2 cells/µl (n=51), respectively ($p<0.01$). Hilar adenopathy was noted in 5 (8%) patients and all but one had CD4+ count <200 cells/µl. Pleural effusion was noted in 10 (16.7%) patients (mean 194.5 ± 82.9/µl). Lower/mid-zone and reticulonodular opacities and normal radiographs occurred in 7 (11.6%), 2 (3%) and 15 (25%) patients with mean CD4+ counts of 236 ± 46.2, 200 ± 42.2, and 173.9 ± 67.8/µl, respectively. It was concluded that radiographic patterns of PTB in HIV varied over a spectrum and may be related to the stage of HIV infection. Hilar adenopathy was the best predictor of low CD4+ counts and atypical radiographic patterns have no predictive value with regard to CD4+ counts.

Key words: HIV, tuberculosis, radiographic patterns, CD4+ cell counts, Nigerians

INTRODUCTION

The recent increase in the prevalence of tuberculosis (TB) globally and particularly in Africa has been attributed to the increase in the

number of human immunodeficiency virus (HIV)-infected patients (1, 2).

Tuberculosis infection may develop at any stage of HIV infection, but most patients have been shown to have CD4+ counts of between 200 and 500/µl (3). Overall, radiographically, patients with higher CD4+ counts often present in "classic" fashion (upper zone infiltrates ± cavities) whereas those with low CD4+ counts are more likely to present atypically. Typical lesions are seen in post-primary TB in immunocompetent hosts and those with CD4+ cell counts closer to normal, while diffuse, lower or mid-zone infiltrates, pleural effusion, mediastinal adenopathy, interstitial nodules or normal radiograph represent "atypical" lesions (4, 5).

Some studies have shown correlation between CD4+ cell counts and the radiographic pattern of pulmonary tuberculosis (4, 5) and mortality risk (6-8). On the other hand, other reports have indicated a lack of correlation between CD4+ cell counts and severity and the extent of lesion radiographically (9-11).

This study was therefore aimed at determining whether a correlation exists between the degree of immunosuppression (CD4+ cell levels) and the various radiographic patterns of pulmonary tuberculosis in our patients with HIV-related pulmonary tuberculosis.

METHODS / PATIENTS

Study design/site: A cross-sectional study carried out using a structured questionnaire at the University of Maiduguri Teaching Hospital, Maiduguri, Nigeria. The questionnaire contained information on demographic data, risk factor (s), clinical and radiological features.

Study subjects: A total of 60 consecutive patients with sputum smear positive pulmonary tuberculosis, positive for HIV antibodies as detected by enzyme-linked immunosorbent assay (ELISA) (Genscreen HIV1/HIV2 version 2. Sanofi-Pasteur) and confirmed by immonocomb II (IMMUNOCOMBFIRM) (HIV1/HIV2 combfirm Orgenics) who presented at the hospital between September 2001 and August 2002 were studied.

Patients on immunosuppressive therapy, antiretroviral therapy longer than one week, antituberculous therapy for more than one month and those who denied consent as well as patients with diabetes mellitus, chronic renal failure, nephrotic syndrome, sickle cell disease and widespread malignancies were excluded from the study.

CD4 T-Lymphocyte counts: Blood specimen for CD4+ counts (Dynal Biotech) was collected during morning hours (10am and 12 noon), from a free-flowing venipuncture site and added to containers with Tri-potassium Ethylene Diethylamide Tetra acetic Acid (K_3EDTA) with the ratio 1-1.5mg of K_3EDTA to one ml of whole blood collected and studied within five hours of collection. Dynabeads CD4, product N0. 111.05, was used for the CD4+ count estimation. The dynal bead technique (Dynal Biotech) was used and the CD4+ cells were counted using 0.1mm deep haemocytometer counting chamber (Neubauer).

Chest radiograph: Standard posteroanterior radiographs were obtained with film-screen at 90–140 KVp in all patients. A consultant radiologist who was blinded to the CD4+ cell count and clinical history reviewed each radiograph. Patients were assigned to one of two groups (typical patterns or atypical pattern). Thoracocentesis was performed in all patients with radiological evidence for confirmation of pleural effusion.

Statistical methods: The data obtained were analyzed using SPSS version 11.0. Values were expressed as mean ± standard deviation (M ± SD). Chi-square test and Student t-test were used to analyze the data. A p value of <0.05 was considered significant.

RESULTS

Thirty four males (56.7%) and 26 females (43.3%) were enrolled into the study. Figure 1 shows the age and sex distribution of the patients. Their ages ranged between 18 and 55 years with a mean (± SD) of 33.9 ± 8.42 years and median of 33 years. The age range with the highest proportion of infected patients was 30-40 years and 20-34 years for males and females, respectively.

The duration of symptoms prior to presentation ranged from 3 weeks to 8 months. Using the 1993 CDC Surveillance Case Definition of AIDS (12), 26 of the patients were in category C3, 32 in C2 and only 2 in C1.

CD4+ T-lymphocyte counts: The CD4+ cell counts ranged between 73 and 512 cells/μl (mean: 238.7 ± 115.9 cells/μl, median: 210 cells/μl). Twenty six (43%) of the patients had CD4+ cell counts <200 cells/μl (mean: 141.5 ± 32.4) while the remaining 34 (57%) had CD4 counts ≥ 200 cells/μl (mean: 313.10 ± 100.3).

Chest Radiographs: The distribution of chest radiographic patterns of PTB and levels of significance across the CD4+ T-lymphocyte count divide is shown in tables 1 and 2. Patients with pleural effusion had a significantly lower mean CD4+ cell count when compared to those with radiographs typical of reactivation PTB ($p<0.01$). The mean CD4+ cell count of pleural effusion was not significantly different from that of other atypical patterns ($p>0.05$). There was a significant difference across the CD4+ cell divide of 200 cells/μl in patients presenting with normal radiographs ($P=0.014$). Fifteen patients (25%) had normal chest radiographs. The difference in mean CD4+ counts between those presenting a radiographically typical versus atypical appearance was statistically significant ($p<0.01$) (table 3).

Figure 2 shows a typical radiograph (apical fibrosis with cavitations) seen in a patient with CD4+ count >200 cells/ul while figure 3 shows an atypical radiograph (Right-sided massive pleural effusion) seen in a patient with CD4+ count < 200 cells/ul.

DISCUSSION

This study has clearly shown that PTB occurred at all stages of HIV infection and it has also clearly demonstrated that patients with CD4+ counts ≥ 200 cells/μl often present with typical radiographic pattern while those with counts <200 cells/μl present atypically.

The mean age of 33.9 ± 8.42 of the patients in this study is similar to the observations of other Nigerian workers (9, 13, 14) and Hsieh *et al* (15) in Taiwan who reported a similar age distribution among HIV–associated PTB patients. This corroborates the fact that HIV is more common in people in their productive and sexually active age groups (16). The male: female ratio of 1.3:1 shows the near unity in sex distribution of HIV infection in Nigeria. However, it differs from the findings of other workers in other parts of the world (17) and Nigeria (9, 13, 14) who reported male preponderance. This may be due in part to the time difference between this and the other studies, which were conducted between 5 and 8 years earlier.

There was a significant difference between patients with typical and atypical radiographic patterns in mean (± SD) CD4+ counts (442.2 ± 89.2 Vs 202.2 ± 77.3) ($p<0.01$). Cell mediated immunity is the limb of the immune system frequently depressed in the HIV-seropositive patients. Thus, with an impaired mechanism for control of TB infection, both an increased incidence of TB as well as an atypical appearance of PTB in AIDS patients is expected. The mean (± SD) CD4+ T-lymphocyte count of 238.7 ± 115.9 was lower than that reported by Habib *et al.* (9) and Idoko *et al.* (18), which suggests that our

patients may be presenting late to Hospital perhaps because of socio-economic reasons or the social stigma associated with both HIV infection and tuberculosis. Using the CDC 1993 revised classification system for AIDS (12), most of the study subjects were in classes C2 and C3 confirming that our patients had severe immunosuppression.

The mean CD4+ count in this study is, however, consistent with that of Lee *et al* (17). The finding of higher mean CD4+ cell count in female patients as compared to the males (242.23±129.5 vs. 236.05±106.2, $p>0.05$) is similar to that of Idoko *et al.*(18) who reported a significantly higher mean CD4+ count in female HIV-infected patients than their male counterparts.

Some of the literature in the past two and half decades have described two general patterns of radiographic presentation of PTB - typical reactivation or post-primary TB and an "unusual" pattern of adult PTB thought traditionally to be limited to TB of childhood (19, 20). These "unusual" patterns associated with PTB in the literature include hilar and mediastinal adenopathy, pleural effusion, miliary disease, pulmonary opacities in the anterior segment of the upper lobes or middle and lower lobes, reticulonodular opacities and a normal radiograph (4, 5).

Reactivation or post-primary TB has been reserved for subjects with upper lobe opacities with or without cavitation and fibrosis (4).

Kolawole *et al.* (21) in Ibadan, Nigeria, reported that the upper lobes were the most affected in PTB but there were also adults with the childhood pattern. Our finding differs from this finding in that normal chest radiograph had the highest frequency among our patients. A plausible reason for this may be because their patients were not HIV-infected and the small number with atypical radiographs were attributed to the high incidence of diabetes mellitus, malnutrition and other infections as well as environmental socio-economic factors. However, none of our patients had any of these diseases, which makes it possible that HIV infection is the most likely culprit.

Atypical radiographic patterns did not reliably predict CD4 + T- cell counts except for hilar adenopathy and normal radiographs, as many patients with CD4+ count 200 cells/μl also had atypical pattern. In agreement with previous reports (5, 22), hilar adenopathy was the best predictor of low CD4+T-cell counts. In this study, hilar adenopathy was common in patients with CD4+ counts <200 cells/μl and had the lowest mean CD4+ cell count (156 ± 66.2) but was unusual in those with higher CD4+ cell counts, confirming the reports by Post *et al.* (5) and Jones *et al.* (22) that HIV- infected TB patients with hilar adenopathy had lower CD4+ cell counts than those without adenopathy. The frequency of pleural effusion in this study is not very different from those of earlier reports which documented frequencies of 10-29% (22, 23). Pleural effusion, though regarded as a marker of early clinical HIV disease (22) occurred throughout an intermediate range of lymphocyte counts and its presence was less helpful for prediction of HIV disease stage.

None of the patients with typical radiographic pattern in this study had CD4+ cell counts <200 cells/μl. The frequency of upper lobe disease was related to CD4+ cell counts. Two patients with upper lobe disease had cavitation. None of those with upper lobe disease CD4+ had CD4+ cell count <200 cells/μl. This is in contrast to the findings of Abouya *et al.* (24) who reported a prevalence of 29% among their patients with CD4+ counts <200 cells/μl who have upper lobe cavitation. However, the finding in this study is similar to those of other workers, which strongly suggests the rarity of cavitary TB in severely immunosuppressed HIV patients (4, 5, 23). This is consistent with experimental data that cavity formation requires an intact delayed type hypersensitivity response and vigorous lymphocyte reactivity to *M. tuberculosis* antigens (25, 26). However, Jones and colleagues (22) reported that the frequency of upper lobe disease was unrelated to the CD4+ cell count. This is not

surprising, as one would not expect the anatomic location of PTB to depend on the CD4+ cell count or on cell-mediated immunity. There may be other unidentified factors that might cause parallel changes in both CD4+ counts and manifestations of TB as being responsible for this.

The finding of normal chest radiograph in 15% of our HIV-related PTB patients is in keeping with that of other workers (4, 17, 21, 27). This, like the other atypical patterns, is related to immune status as immunosuppressed patients cannot mount adequate immune response to *M. tuberculosis* which is responsible for the radiographic lesions seen in these patients.

The results of this study have shown that PTB occurred at all stages of HIV infection and that there might be a spectrum of chest radiographic presentation related to HIV disease stage. HIV/TB Patients CD4+counts (200 cells/μl) tend to present with "typical" radiographic patterns while those with counts <200 cells/μl present with atypical patterns. Hilar adenopathy was the best predictor of low CD4+ T-cell counts.

The CD4+ counts did not reliably predict those that will present with atypical radiographic patterns. Larger studies are needed to determine the predictive values of the various radiographic patterns of HIV disease stage.

REFERENCES

1. Rogeaux O. Bricaire F, Gentilini M. Tuberculosis and HIV. Rev Med. Interne. 1993; 14(7): 715-722.
2. Perriens JH, Mukadi Y, Nunn P. Tuberculosis and HIV infection: Implications for Africa. AIDS 1991; 5 (suppl1) S127 - S133.
3. Kayembe KP, Nelson AM, Colebunders RL. Opportunistic infections and diseases. In: Max E, Mboup S, Kanki PJ. (eds) AIDS in Africa, Raven press, New York, 1994; 373 -391.
4. Keiper MD, Beumont M, Elshami A. CD4+ T-lymphocyte count and the radiographic presentation of pulmonary tuberculosis (in HIV). Chest 1995; 107:74-80
5. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV Infection: Radiographic appearance is related to CD4 + T lymphocyte counts. Tubercle and lung Disease 1995; 76:518 - 21.
6. Ackah AN, Coulibaly D, Digbeu H. Response to treatment, mortality and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. Lancet 1995; 345:607 – 10
7. Yarchoan R, Mitsuya H, Broder S. The immunology of HIV infection: implications for therapy. AIDS Res Hum Retro-viruses 1992; 8:1023 – 31
8. Shearer W T, Rosenblatt HM, Schlucter MD. Immunologic targets of HIV infection: T-Cells. NICHD IVIG clinical trial group. Ann NY Acad. Sc. 1993;
9. Habib AG, Keshinro IB, Gebi UI. Clinical presentation of HIV infection in Nigeria and its relationship to CD4 + T - cell counts. Nig Med Pract. 1998; 35:3 - 8.
10. Qin J. NK cell activity and counts of T-lymphocyte subsets in pulmonary tuberculosis. Chung-Hua Chieh - Hoho Hutsi - Tsachin 1990; 13:209 - 11,254
11. Habib AG. Assessment of cell-mediated immunity and clinical correlates in pulmonary tuberculosis. *West African College of Physicians (FWACP) thesis*, 1993.
12. Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR. 1992; 41 (RR - 17): 1 – 19
13. Idoko JA, Anteyi EA, Idoko LO. HIV and associated TB in Jos, Nigeria. Nig Med Pract 1994; 28:24 - 50
14. Wokoma FS. HIV status of adult Nigerian patients suffering from pulmonary tuberculosis. Nig Med Pract 1997; 34:22 - 24.
15. Hsieh SM, Hung CC, Chen MY, Chang SC, Hsueh PR, Luh KT, Chuang CY. Clinical features of tuberculosis associated with HIV

infection in Taiwan. J Formos Med Assoc 1996; 95(12): 923-8
16. Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull World Health Organ 1994; 72: 213-220.
17. Lee MP, Chan JW, Ng KK, Li PC. Clinical manifestations of tuberculosis in HIV-infected patients. Respirology. 2000; 5 (4): 423-6.
18. Idoko JA, Sirisena ND, Isamade EI. CD4+ lymphocyte counts in human immunodeficiency virus-infected and healthy Nigerian population. Nig. Med Pract 2001; 39 (3/4): 53-56
19. Law KF, Jagirdar J, Weiden MD. Tuberculosis in HIV-positive patients: cellular and immune activation in the lung. Am J Respir Crit Care Med. 1996; 153 (4pt 1): 1377 - 1384.
20. Kaur A, Babu PG, Jacob M. Clinical and laboratory profile of AIDS in India. J. AIDS 1992; 5: 883 - 889
21. Kolawole TM, Onadeko BO, Sofowora EO, Esan GE. Radiological patterns of Pulmonary tuberculosis in Nigeria. Trop Geogr Med 1975; 27: 339-350
22. Jones BE, Young SMM, Antoniskis D. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with HIV infection. Am Rev Respir Dis 1993; 148: 1292-1297.
23. Pitchenik AE, Rubinson A. The radiographic appearance of tuberculosis in patients with the Acquired Immunodeficiency Syndrome (AIDS and pre-AIDS). Am Rev Respir Dis 1985; 131: 393-6
24. Abouya L, Coulibaly IM, Coulibaly D, Kassim S, Ackah A, Greenberg AE, Wiktor SZ, De Cock KM. Radiologic manifestations of pulmonary TB in HIV-1 and HIV-2-infected patients in Abidjan, Cote d'Ivoire. Tuber Lung Dis. 1995; 76 (5): 436-40.
25. Dannenberg AM Jr. Immune mechanisms in the aetiopathogenesis of pulmonary TB. Rev Inf Dis 1989; II (52): S369-383.
26. Dannenberg AM Jr, Tomashefski JF Jr. Pathogenesis of pulmonary tuberculosis. In: Fishman AP, (ed). Pulmonary Diseases And Disorders. 2nd edition. New York: McGraw Hill, 1988: 1821-42.
27. Pitchenik AE, Cole C, Russel BW, Fischl MA, Spira TJ, Snider DE. Tuberculosis, atypical mycobacteriosis, and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. Ann Intern Med 1984; 101:641-5

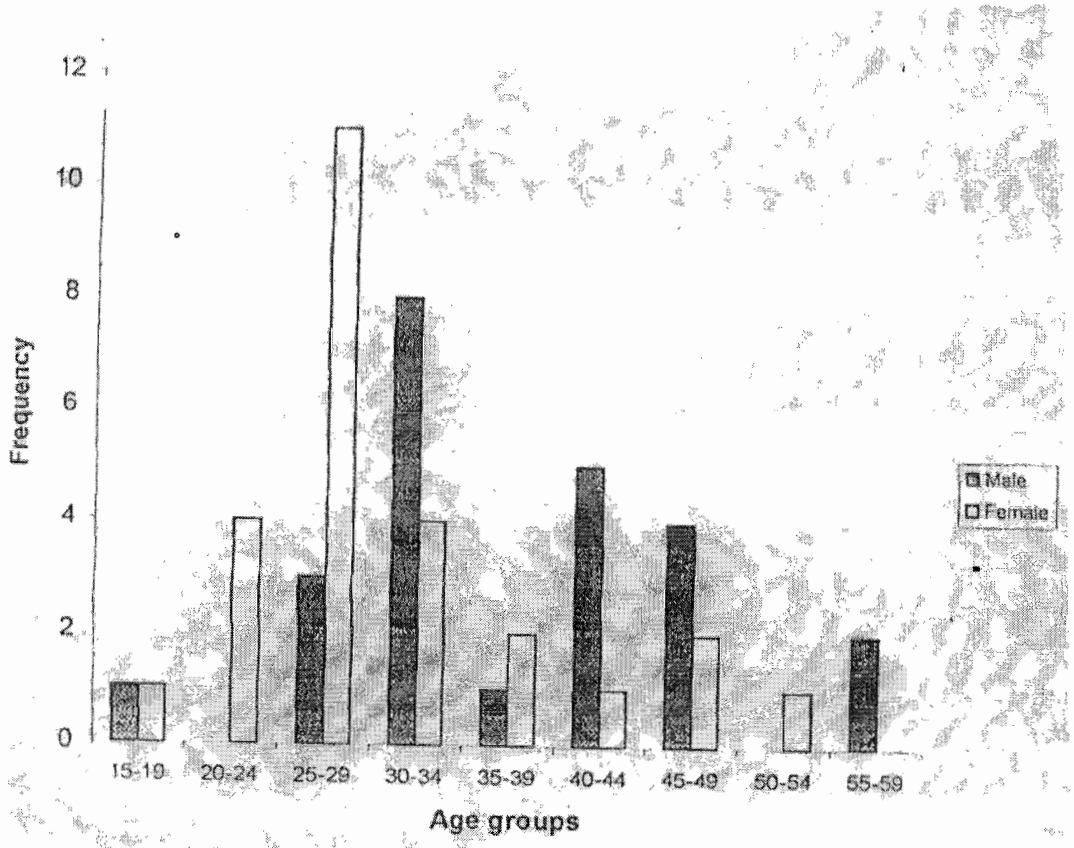

Fig.1. Age and sex distribution of study patients

Table 1. Chest x-ray patterns and corresponding mean CD4 counts

Radiographic Pattern	Frequency	Percent	Mean CD4 count ± SD
Apical opacity/cavitation	9	15	442.2 ± 89.2
Lower/mid zone opacity	7	11.7	243.4 ± 44.4
Miliary opacities	12	20	242.2 ± 84.4
Reticulonodular shadows	2	3.3	200 ± 42.4
Pleural effusion	10	16.7	194.5 ± 82.9
Normal	15	25	173.9 ± 67.8
Hilar adenopathy	5	8.3	156 ± 66.2

Table 2. Levels of significance in the differences of radiographic patterns in relation to CD4+ counts

Radiographic pattern	CD4+ cell counts (/ul)		P value	Total
	<200	200		
Apical opacity	0	9	0.004**	9
Normal	11	4	0.014**	15
Miliary	3	9	0.21	12
Pleural effusion	6	4	0.305	10
Lower/mid-zone opacity	1	6	0.126	7
Hilar adenopathy	4	1	0.156	5
Reticulonodular shadows	1	1	1.000	2
Total	26	34		60

**Significant at the 0.05 level (Fisher's exact test).

Table 3. Correlation of chest x-ray patterns with CD4 counts

	CD4 counts/µl				
Radiographic pattern	<200	≥ 200	Mean CD4 count	*p* value	Total
Typical	0	9	442.2 (89.2)	0.004*	9
Atypical	26	25	202.8 (76.2)		51
Total	26	34			60

*Significant at the 0.05 level (Fisher's exact test).

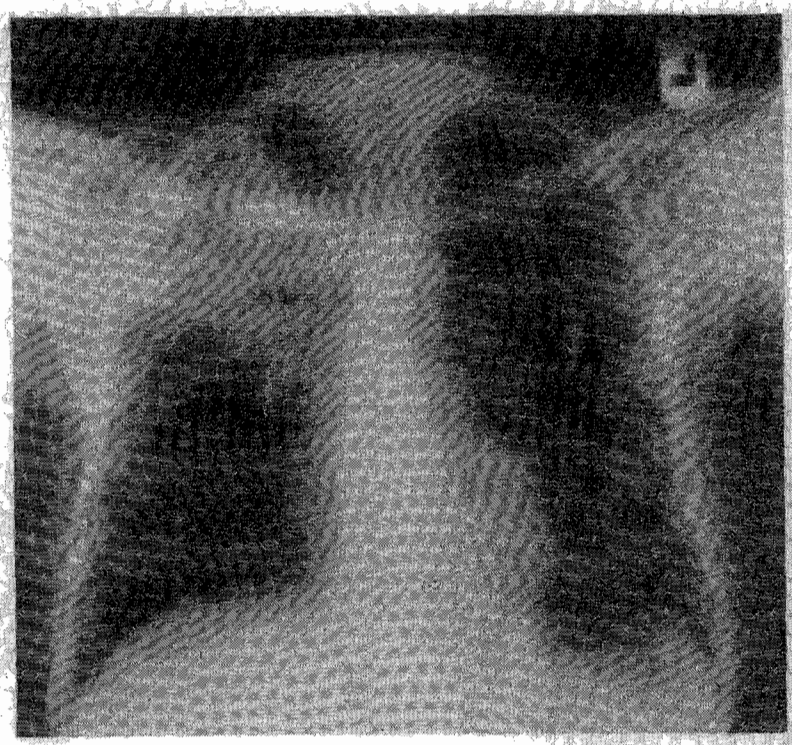

Fig. 1. Chest x-ray showing right apical opacity with cavitations in HIV/PTB patient with CD4 count ≥200 cells/μl

Fig. 2. Chest x-ray showing right pleural effusion in HIV/PTB patient with CD4 count <200cels/µl