STUDY OF 17 PATIENTS WITH TUBERCULOSIS AND HIV INFECTION

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Abstract- ***Tuberculosis is an important opportunistic disease among HIV-infected persons worldwide. From March 1999 to Feburery 2001 we had seventeen patients with HIV-infection and tuberculosis. Here we are presenting the clinical manifestations, diagnosis, treatment and outcome of them. All of them were male, 11 patients had pulmonary and 5 patients had extrapulmonary (pleural effusion 1, hepatic granulomatosis 1, lymphadenopathy 3), one patient had pulmonary and polyserositis tuberculosis. Tuberculin skin test was positive in 6 paitents and only six patients had CD4 cell count at the beginning of their disease. Thirteen patients had positive smear for acid fast bacilli and four paitents had pathology compatible with tuberculosis (caseating granulomatous). Three patients were hemophiliac, nine patients were injecting drug users, fourteen paitents were treated with 6 months regimens and five patients died. Six patients had the scar of BCG vaccination and others did not know anything about it.***

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Key Words: HIV, AIDS, tuberculosis, CD_4^+ T cells, tuberculin test

INTRODUCTION

Tuberculosis remains an important problem in patients with human immunodeficiency virus (HIV) in the world (1). HIV-infected persons are at markedly increased risk of primary or reactivation tuberculosis and for second episodes of tuberculosis from exogenous reinfection (2,3). Susceptibility to tuberculosis is related to the pattern of cytokines produced by T lymphocytes. Th_1 lymphocytes, which produced interferon-γ are central to antimycobacterial immune defenses and fatal mycobacterial disease develops in childern who lack the interferon-γ receptors (4). In contrast to T_1 lymphocytes, Th_2 lymphocytes, which produce interleukin-4 and interleukin-10, do not contribute to antimycobacterial immunity (5). When peripheral blood lymphocytes from HIV-infected patients with tuberculosis are exposed to mycobacterium tuberculosis in vitro, they produce less interferon-γ but similar amounts of interleukin-4 and interleukin-10 as compared with lymphocytes from HIV negative patients with tuberculosis (6). These findings suggest that the reduced Th_1 response in HIV-infected patients contributes to their susceptibility to tuberculosis (2,7). Mycobacterium tuberculosis probably increases HIV replication by inducing macrophages to produce tumor necrosis factor alfa, interleukin-1 and interleukin-6 (7,8,9). Clinical studies have shown, the risk of death in HIV infected patients with tuberculosis as twice that of HIV-infected patients without tuberculosis (2,7,10).

The high mortality rate among patients with tuberculosis appeared to be due to progressive HIV infection rather than tuberculosis. The degree of immunosuppression is the most important predictor of survival in HIV-infected patients with tuberculosis, since negative tuberculin skin test, prior opportunistic infections, and low CD_4 cell counts are associated with increased mortality (11,12).

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PATIENTS

Patient 1: A 44-year old driver man was admitted with cough, sputum and weight loss. About 20 days previously, he was admitted in Karaj hospital with diabetic hyperosmolar coma. He had insulin dependent diabetes mellitus for 7 years. He has been opium and cigarrete user for the past 20 years ago. He had been in prison five years ago for 5 months. On physical examination, he was cachectic, fine crackles in upper lobes of lungs. CBC, U/A, liver enzyme, were normal and tuberculin test was negative. In chest X-Ray, reticulonodular infiltration with cavities were seen in both upper lobe. Sputum smear for acid fast bacilli(AFB) was positive. Antituberculosis therapy with 4 drugs isoniazid, rifampin, pyrazinamide and ethambutol (HRZE) along with vitamine B6 was begun, as he didn't get weight although sputum smear became negative after one month.We decided to check HIV test, which was positive and he worked up for initial approach to HIV infection and was discharged while he continued to take antituberculosis drugs and insulin (NPH).

Patient 2: A 32-year old man was admitted with fever, cough and sputum for 4 months. He had malaise, weight loss(12 kg), night sweats and vesicular rash on extremities for 3-4 months.

He went to Thailand 8 years ago, and he had multiple sexual contacts in Thailand and Iran. Two months before admission the HIV test was positive. On examination: T= 38, PR= 96, RR= 24, BP= 90/60. There were multiple, mobile, nontender lympha- denopathy in posterior cervical and axillary regions. The chest, abdomen and extremities were normal. WBC, PLT, LFT, liver enzyme, U/A, BUN, Cr were normal, Hb= 8.5 Hct= 25%, CD4= 10/mm^3. On chest X Ray there were paratracheal lymphadenopathy and diffuse reticulonodular infiltration, sputum smear was positive for acid fast bacilli. Then antituberculosis therapy with 4 drugs had begun. Five days after admission blood cultures (3 times) were positive for Cryptococcus neoformans. Lumbar puncture was done and in CSF there was 33 mg% protein, 75 mg% glucose, 100 WBC, RBC= 30000. CSF culture was positive for Cryptococous neoformans. Amphotericin B and fluconazole were added to treatment with attention to interaction of fluconazole with rifampin. After one week fever abated and he had good condition, so he was discharged with fluconazole and antituberculosis drugs. He received antituberculosis therapy for 9 months. One year later he came to hospital with headache and right foot paresthesia. In brain MRI, there were multiple lesions with ring enhancement. So he received anti toxoplasmosis drugs (sulfadiazine and pyrimethamine) with fluconazole. He died in deep coma 2 weeks later.

Paitent 3: A 50-year old man was referred for generalized lymphadenopathy and positive anti HIV test. He had a history of injecting drug use for 10 years and had been a prisoner 3 years ago for 9 months and shared syringe. On examination, T=37.5°C PR, RR and BP were normal, there were multiple lymphadenopathy 1×1 and 1×2 centimeters in right and left posterior cervical and both axillary and inguinal. Results of chest, abdomen, extremities and neurological examination were normal. CBC, U/A, liver enzyme, blood chemistry were normal. Anti Hepatitis C virus (anti HCV) was positive. HBsAg was negative but anti HBc was positive, Tuberculin test was positive (Induration= 12mm), chest X Ray was normal, biopsy of axillary lymph node showed: Caseating necrotizing granulomatous reaction, so treatment with HRZE was begun and followed up for 2 months.

Patient 4: A 47-year old man was admitted with cough, sputum, pleuretic chest pain, low grade fever, night sweat and 12 kg weight loss. He had been in prison since 2 years ago for injecting drug. On examination T= 38, PR= 80, RR= 22, mild anemia, and fine crackle in left upper lobe. CBC, blood chemistry, U/A and liver enzyme were normal, tuberculin test was negative. Chest X Ray showed left upper lobe reticulonodular infiltration with cavity formation, HIV antibody test was positive, sputum smear was positive in three times for acid fast bacilli. Treatment with HRZE was begun.

Patient 5: A 23-year old man was admitted with fever, dyspnea and weight loss. He had been a haemophilic man and HIV positive for 10 years before admission. Three years ago his tuberculin test was positive (8 mm induration) but he didn't use isoniazid. On examination: T=38.5, RR=30, PR=90 and BP=140/70, anemia, post nasal drip, cachexia and decreased breath sound in right lung. Chest X ray showed free right sided large pleural effusion. Pleural effusion was exudative and smear for acid fast bacilli was positive, tuberculin test had 9 mm induration and CD_4 T-cells count was 150/mm^3. The antituberculosis therapy with HRZE was begun but he didn't tolerate them, he vomited the drugs so the drugs were administered in low doses and raised slowly in about 10 days and completed the total course of 9 month. 2 years later he was admitted with a large mass in his brain and died.

Patient 6: A 40- year old injecting drug user man was admitted for fever and icterus. He was in prison 6 years ago for 3 years and he shared his needle with other prisoners. HBsAg, HIV and HCV tests were positive. On examination: T=38.5, PR=120, RR=18, BP=130/70, mild anemia and icterus were noted in his sclera, chest was normal, abdomen was soft, had no organomegaly, and no ascites. WBC=5200, poly= 70%, lymph= 28% and mono= 2%, Hb= 10.6, Hct= 31%, CD4= 150/mm^3. Chest X Ray was normal, abdominal sonography was normal, PPD= 12mm, ALT= 120, AST= 125, AlkPh= 490, PT= 90% total Bil= 5, Dir= 3, liver biopsy showed: Caseating granulomatous lesions. Antituberculosis therapy with HRZE was begun and the patient was discharged 2 weeks later, while he continued to take antituberculosis drugs.

Patient 7: A 39-year injecting drug user man from prison was admitted with cough, fever, malaise, weight loss and decreased level of consciousness. He had been in prison for 5 years and had been injecting drug for 15 years. On examination: T= 38.3, PR= 100, RR= 28, BP=100/80, very ill patient with cachexia, anemia, icter in sclera, oral candidiasis, crackle in both lungs, splenomegaly 2-3 cm in subcostal margin, shifting dullness in abdomen, petechia and purpura in both feet and neurological exam was normal. WBC= 3400, Poly= 84%, lymph= 14%, CD4= 50, Hb= 7, Hct= 20%, PT=18 (control 13), PTT=80, AST=262, ALT= 46, AlKPh= 727, K= 2.1, Na= 125, Total Bil= 30.03, Direct= 25, CXR showed diffuse reti- culonodular infiltration with right side pleural effusion. Pleural effusion and ascites were exudative fluid, tuberculin test was negative, brain CT scan was normal and brain CT scan and CSF analysis were both normal. CSF was also normal.

Sputum smear and gastric lavage were negative for acid fast bacilli. Bone marrow biopsy showed: necrotizing granulomatous reaction with giant cell and lymphoplasmocytes. Anti-TB (HRZE) and dexamethazone were begun. But the patient revealed no response and died 10 days later.

Patient 8: A 39-year old injecting drug user from prison was admitted with cough, sputum and cervical mass. He has been in prison since 13 years ago. Cough and white sputum began from 6 months and left cervical mass from 4 months before admission. On examination: T= 37.5°, PR= 70, RR= 22, BP=100/90, very ill, cachectic patient, anemia, oral thrush, left anterior cervical mass 4×5×3cm, fine crackles in both base lungs. Tests for HIV, HCV and HBsAg were positive, WBC=2300, poly=81%, Lymph= 17%, CD4= 2%, CD4= 8/mm3, CD8= 40%, sputum smears for acid fast bacilli were negative (3 times). Liver enzymes and liver function tests were normal. Tuberculin test was negative, CXR showed reticular pattern in both lung bases. Cervical mass was aspirated and its smear showed large number of acid fast bacilli on ziehl-neelsen stain. Therapy with HRZE was started and 3 weeks later with good condition he was discharged, to continue the medications.

Patient 9: A 42-year old haemoplilic and HIV - infected man visited for large anterior cervical mass of 2 weeks duration. On examination: very thin man with large right cervical mass (10×10 cm) and some lymphadenopathy on posterior cervical chain. Chest, abdomen and extremities were normal. Excisional biopsy of mass was done and smear for acid fast bacilli was positive and its pathology showed granulomatous reaction. He recieved antiretroviral drugs (zidovudine, lamivudine and indinavir) so antituberculosis drugs were isoniazid, ethambutol and pyrazinamide. Tuberculin test was positive (12 mm induration). The symptoms and signs of other patients are summerized in table 1.

Table 1. Features of tuberculosis in relation to HIV-infected patients

No	Six/age	XP Site	involved Site	Both	Tuberculin test	CD_4/mm^3	Concomitant Desease	Diagnosis AFB+/ pathology	Route of HIV transmission	Outcome
1	M/44	×			-ve	?	Diabetes	AFB[1]	IDU[2]	Good
2	M/32	×			-ve	10	Crptococcosis	AFB	Sexual	Died
3	M/50		×		+ve	?	HCV[3]	Pathology	IDU	?
4	M/47	×			-ve	?	---	AFB	IDU	?
5	M/23		×		+ve	150	---	AFB	Hemophiliac	Died
6	M/40		×		+ve	?	HBV[4]/HCV	Pathology	IDU	Good
7	M/39	×	×	×	-ve	50	Oral candidiasis	Pathology	IDU	Died
8	M/39		×		-ve	8	HBV,HCV	AFB	IDU	Good
9	M/42		×		+ve	?	HCV	AFB	Hemophiliac	Good
10	M/47	×			+ve	?	Diarrhea	AFB	IDU	Good
11	M/35	×			-ve	?	?	AFB	IDU	Good
12	M/30	×			-ve	?	HCV	AFB	IDU	?
13	M/49	×			-ve	?	?	AFB	IDU	?
14	M/60	×			+ve	?	?	AFB	Sexual	?
15	M/41	×			-ve	50	CMV retinitis	AFB	Sexual	Died
16	M/25		×		-ve	Zero	---	Pathology	Hemophiliac	Died
17	M/40	×			-ve	?	PCP	AFB	Sexual	good

1: AFB= Acid Fast Bacilli
2: IDU= Injecting Drug User
3: HCV= Hepatitis C Virus
4: HBV= Hepatitis B Virus
Pul: Pulmonary
XP: extrapulmonary

Table 2. Fratures of clinical tuberculosis in relation to HIV infection and immunosuppression

Clinical features	HIV negative	Early HIV	Advanced HIV
TST[1]	>10mm 75-80% positive	>10mm 40-70% positive	>10mm 10-30% positive
CXR[2]	50-70% typical upper lobe fibronodular 50% cavities	Mixed typical And atypical	Adenopathy Effusions Lower zone and miliary no cavitation
Sites involved	Pulmonary 80% Extrapulmonary 16% both 4%	intermediate	Pulmonary 20-30% Extrapulmonary 20-50% Both 30-70%

1) Tuberculin Skin Test 2) Chest X Ray

DISCUSSION

It is estimated that there are 40 million persons infected with HIV globally and that nearly 6 million of these persons are also infected with mycobacterium tuberculosis (14). In our hospital there were 17 cases of tuberculosis and AIDS who were admitted. The typical features of tuberculosis occuring early and late in the course of HIV infection are displayed in table 2 (7,14-18). As the level of immunosuppression increases in HIV-infected patients, mycobacteremia and extra- pulmonary tuberculosis become progressively more common (13). In our series, all of them were male, nine of them were injecting drugs and five of them were in prison. Ten of our patients had pulmonary and five of them had extrapulmonary tuberculosis (pleural effusion 1, granulomatous hepatitis 1, lymphadeno-pathy 3). One of our patients (No. 7) had pulmonary and polyserositis tuberculosis. We hadn't any CD_4^+ T cells count in 11 patients to determine the stage of their disease. The typical features of tuberculosis in early HIV-infection is pulmonary with positive tuberculin test (40-70%), typical pulmonary infiltration on chest X-Ray and positive sputum smear (50-60%). But in advanced AIDS, tuberculin tests are positive in (10-30%), generalized adenopathy, miliary and atypical pulmonary infiltration in chest X-ray in 20-50%, pulmonary and extrapulmonary tuberculosis are common (30-70%) but sputum smear are positive in only 30-40% (15-18). In patients who have CD_4^+ T cell counts of 200/mm^3 or more, chest X-Ray findings included upper lobe infiltration and cavitation as in our patients No: 1,10,11,12.13,14. In our patients who have CD_4^+ T cell count fewer than 200/mm^3, mediastinal adenopathy, miliary patterns are common findings in chest X-Ray (17,18). Approximately 5% of HIV infected patients with pulmonary tuberculosis had positive results on acid-fast staining of sputum, despite normal chest X-Ray as in patients 13 and 17 (14,17,19).

In HIV infected patients with drug susceptible tuberculosis, the standard six-month regimen results in prompt sterilization of sputum and low rates of treatment failure, similar to HIV-negative persons (2,7,14,20). The longer regimens may have provided more effective treatment or may have prevented exogenous reinfection (21,22). Fifteen of our patients recevied HRZE but only one patient who had haemophiliae, as treated with antiretroviral therapy (zidovudine, lamivudine and indinavir), didn't get rifampin. The clinical and bacteriological response of our patients was good and we didn't change or prolong the regimen. If the clinical or bacteriological response is slow in HIV-infected patients, treatment should be given for a total period of nine months, or for four months after culture becomes negative (4,23). Direct observed therapy (DOT) improves the outcome. It is cost effective and strongly recommended for HIV infected patients (22,24,25). But we couldn't give antituberculosis drugs by DOT. New antiretroviral combination regimens have dramatically improved the prognosis of HIV-infected patients but have complicated the management of tuberculosis. Rifampin induces the activity of cytochrome P450 CYP3A which lowers the concentration of HIV-protease inhibitors, and non-nucleoside reverse-transcriptase inhibitors to subtherapeutic levels. So incomplete viral suppression and emergence of drug resistance, therefore concomitant administration of rifampin with these drugs is not recommended (2,14,26,27). In patient 9, therapy with isoniazid, pyrazinamide and ethambutol was started as he had received antiretroviral therapy. HIV-infected patients with recent or remote M. tuberculosis infection are at extremely high risk for developing tuberculosis. Once active tuberculosis has been ruled out, chemoprophylaxis is recommended. Isoniazid for 6 months or isoniazid and rifampin for 3 months or rifampin and pyrazinamide for 2 months are equally effective in preventive therapy (28-31). In conclusion the coepidemie of HIV infection and tuberculosis poses major challenges for global health.

Tuberculosis is also prevalent, in Iran. In any HIV infected patient, specially injecting drug users and in prisons, we must be conscious about tuberculosis.

REFERENCES

1. Markowitz N, Hansen NI, Hope well pc et al. Incidence of tuberculosis in The United State among HIV-infected persons. Ann Intern Med 1997; 126: 123-132.

2. Havlir DV, Barnes PF. Tuberculosis in patients with HIV infection. N Engl J Med 1999; 340: 367-373.

3. Small PM, Shafer RW, Hopewell PC, et al. Exogenous reinfection with multi-resistant Mycobacterium tuberculosis in patient with advanced HIV infeetion. N Engl J Med 1993; 328: 1137-1144.

4. Newport MJ, Huxley CM, Huston S. A mutation in the interferon-γ-receptor gene and susceptibility to mycobacterial infection. N Engl J Med 1996; 335: 1941-1949.

5. Barnes PF, Modlin RL. Human cellular immune responses to Mycobacterium tuberculosis. Curr Top microbiol Immunol 1996; 215: 197-219.

6. Zhang M, Gong J, Iyer DV, Jones BE. T cell cytokine responses in person with tuberculosis and HIV infeetion. J Clin Invest 1994; 94: 2435-42.

7. A clinician's Guide to tuberculosis 2000; p: 199-254.

8. Goletti D, Weisman D, Jackson RW. Effect of Mycobacterium Tuberculosis on HIV replication. J Immunol 1996; 157: 1271-1278.

9. Garrait V, Cadranel J, Esvant H. Tuberculosis generates a microenvironment enhancing the productive infection of local lymphocytes by HIV. J Immunol 1997; 159: 2824-30.

10. Whalen C, Horsburgh CR, Hom D, Lahartc. Accelerated course of HIV infection after tuberculosis. Am J Respir Crit Care Med 1995; 151: 129-35.

11. Whalen C, Okwera A, Johnson J. Predictors of survival in HIV infected patients with pulmonary tuberculosis. Am J Respir Crit Care Med 1996; 153: 1977-81.

12. Whalen C, Horsburgh CR, Hom D. Site of disease and opportunistic infection predict survival in HIV associated tuberculosis. AIDS 1997; 11: 455-460.

13. Jones BE, Young SM, Antoniski D. Relationship of the manifestation of tuberculosis to CD4 cell counts in patients with HIV infection. Am Rev Respir Dis 1993; 148: 1292-1297.

14. Schluger NW. Issue in the treatment of active tuberculosis in HIV infected patients. CID 1999; 28, 130-5.

15. Fee MJ, OoMM, Gabayan AE, Radin DR. Abdominal tuberculosis in patients infected with HIV. Clin. Infect Dis 1995; 20: 938-944.

16. Dube MD, Holtom PD, Larsem RA. Tuberculosis Meningitis in patients with and without HIV infection. Am J Med 1992; 93: 520-524.

17. Perlman DC, Sadr WM, Nelson ET. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immuno- suppression. Clin Infect Dis 1997; 25: 242-246.

18. Jones BE, Ryn R, Yang Z. Chest radiographic finding in patients with tuberculosis with recent or remote infection. Am J Respir Crit Care Med 1997; 156: 1270-73.

19. HAAS, DW. Mycobacterial tuberculosis Mandell, Douglas, and Bennett's principles and practice of infectious disease 2000; 5 th edition 2576-2607.

20. Shafer RW, Edlin BR. Tuberculosis in patients infected with HIV. Clin Infect Dis 1996; 22: 683-704.

21. Hopewell PC. Tuberculosis in persons with HIV infection. Semin Respir Crit Care Med 1997; 18: 471-84.

22. American Thoracic society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000; 161: S221-S247.

23. Prevention and treatment of tuberculosis among patients infected with HIV. MMWR, Morb Mortal wkly Rep 1998; 48: 1-58.

24. Alwood K, Keruly J, Moore-Rice K. Effectiveness of supervised, intermitent therapy for tuberculosis in HIV-infected patients. AIDS 1994; 8: 1103-1108.

25. Iseman MD, Coh DL, Sbarbaro ZA. Directly observed treatment of tuberculosis. N Engl J Med 1993; 328: 576-578.

26. Centers for Disease Control, Clinical update impact of HIV protease inhibitors on the treatment of HIV-infected tuberculosis patients with rifampin MMWR 1996; 45: 921-925.

27. Flexner C. HIV-protease inhibitor. N Engl J Med 1998; 338: 1281-1292.

28. Cox SR, Herman BD, Botts DH. Delarirdine and rifabutin pharmacokinetic evaluation in HIV-1 patients conference on retroviruses and opportunistic infections, 0.0Chicago Feb 1-5, 1998.

29. Halsey NA, Coberly JS, Desormeaus J. Randomized trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet 1998; 351: 786-792.

30. Sepkowitz KA. Effect of prophylaxis on the clinical manifestation of AIDS-Related opportunistic infection. Clin Infect Dis 1998; 26: 806-810.

31. Kevin M, Decock, Eve Lackretz. HIV infection and AIDS Hunter's tropical medicine and emerging infections disease 2000; 8th edition, 176-192.