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Original Article

Pulmonary Manifestations in Human Immunodeficiency Virus Infected Patients and Correlation with CD4 Count: A Clinical Observational Study

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Abstract

Introduction: Pulmonary manifestations are common in patients with human immunodeficiency virus (HIV) infections. In this study, we attempt to evaluate the various pulmonary manifestations and its correlation with CD4 count from a tertiary center in the low prevalence state of Kerala.

Materials and Methods: A total of 56 patients with HIV infection presenting with respiratory symptoms were evaluated and investigated for 24 months.

Results: Out of the 56 patients, 36 were diagnosed to have pulmonary tuberculosis (TB). 18 had smear positive TB, 18 smear negative TB, 13 *Pneumocystis* pneumonia, 3 bacterial pneumonia, no definite etiology identified in 5. The mean CD4 count was lower in smear positive TB patients than in smear negative.

Conclusion: The most common opportunistic respiratory infection in HIV-infected individuals was pulmonary TB (63%). The mean CD4 count in patients with smear positive TB was significantly lower than that of smear negative TB.

Key words: CD4 counts, Human immunodeficiency virus infected, Pulmonary manifestations

INTRODUCTION

The lungs are the major target organs in patient with human immunodeficiency virus (HIV) and in patients with the acquired immunodeficiency syndrome (AIDS). In developed countries, the use of highly active antiretroviral therapy (HAART) and prophylaxis against *Pneumocystis* pneumonia (PcP), *Mycobacterium tuberculosis* (MTB), and *Mycobacterium avium* complex has changed the spectrum of disease affecting the lungs. In these countries in the pre-HAART era, 65% of patients had evidence of pulmonary disease. PcP was the most common cause followed by TB, fungi and bacterial pneumonia. Now there are fewer cases of opportunistic infections, and pulmonary symptoms are more often due to noninfectious complications.

In the developing world, the situation has not changed much. The major cause of pulmonary morbidity and mortality is still attributable to opportunistic infections, with TB being the prime culprit.

India has the third largest HIV epidemic in the world. In 2015, HIV prevalence in India was an estimated 0.26%. The states with high HIV prevalence rates include Manipur (1.40%), Andhra Pradesh (0.90%), Mizoram (0.81%), Nagaland (0.78%), Karnataka (0.63%), and Maharashtra (0.55%).

The state of Kerala comes under the category of low prevalence states. Although there have been a few studies on pulmonary manifestations of HIV infection from the high and moderate prevalence states, there are not many studies focusing on this aspect from the state of Kerala.

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This particular study, therefore, attempts to evaluate the various pulmonary manifestations in HIV-infected patients and its correlation with CD4 count from a tertiary referral center in North Kerala.

MATERIALS AND METHODS

Setting
Institute of chest diseases, Medical College, Calicut.

Period of Study
24 months.

Study Design
Observational study.

Inclusion Criteria
All patients diagnosed to have infected with HIV presenting with respiratory symptoms.

All patients presenting with respiratory symptoms, subsequently, found to be infected with HIV.

Exclusion Criteria
Patients who had other reasons for immunosuppression.

A total of 56 patients with respiratory symptoms were admitted and evaluated. If already diagnosed to have HIV infection, the diagnosis was confirmed by repeated testing. The study population consisted of all adults more than 15 years. Patients were evaluated using a pre-designed pro forma regarding the demographic characteristics, risk factors for HIV infection, presenting symptoms, physical findings, and laboratory parameters. Using the history and investigations available including CD4 counts, all efforts were made to reach at a possible diagnosis for the patient's symptoms. All patients were counseled and offered antiretroviral therapy, whenever indicated. On discharge from the hospital, patients were advised to follow-up as outpatients, on a regular and as needed basis.

RESULTS

The following are the observations made in 56 patients over the study period of 2-year.

Age
The mean age at presentation was 39.3. The maximum number of patients belonged to 21-40 age group (59%) (95% confidence interval = 44.1-70-9).

Sex
The ratio of males to females was 3:1.75% of the study group was formed by males, 25% by females.

Symptoms in the Study Group
The most common symptom at the presentation was cough, which was followed closely by fever and dyspnea.

Symptoms in TB Patients
The most common symptom in patients with TB was fever (92%) and cough (89%) followed by weight loss, which was also seen in 58% of the patients.

Diagnosis
Out of 56 patients, 36 patients had a diagnosis of pulmonary TB. Smear positive TB was diagnosed if the patient's sputum, pleural fluid or lymph node smear (along with respiratory symptoms and chest radiological abnormalities) was positive for acid-fast bacilli. Smear negative TB was diagnosed based on symptoms along with suggestive chest radiological abnormalities, positive tuberculin test (>5 mm) or a favorable response to anti-TB treatment. 18 patients had smear positive TB and 18 had smear negative TB.

PcP was diagnosed if the patients had the organism demonstrable from the sputum, or symptoms or recent onset fever, rapidly progressive dyspnea, dry cough along with suggestive radiological features and a favorable response to cotrimoxazole. 13 patients were diagnosed to have PcP, out of which in 2 patients the organisms was demonstrable from sputum. One patient who had PcP presented 1 year later with features of left pleural effusion and his sputum was positive for acid-fast bacilli.

About 3 patients had a diagnosis of bacterial pneumonia. This was diagnosed based on the clinical features and isolation of organism from the sputum along with radiological abnormalities. In 2 patients, pneumococci were isolated, and in 1 patient, *Klebsiella* species was isolated. One patient with pneumococcal pneumonia gave a history of similar episode 8 months back (recurrent pneumonia) and the other 2 patients had a history of TB and had evidence of fibrosis in their chest radiograph.

No definite diagnosis was possible in 5 patients in spite of all the available investigations. They had respiratory symptoms but no chest radiological abnormalities.

Most of the patients with smear positive TB had upper zone shadows (44%), 3 had mid zone shadows, 3 had pleural effusion, 2 had lower zone infiltrates, and one each had hydropneumothorax and miliary shadows.

In smear negative TB, the most common chest radiological abnormality seen was hilar prominence (28%) and pleural effusion (28%). 4 patients had lower zone shadows, 2 had mid zone shadows, one each had upper zone infiltrates and miliary shadows.

In PcP, 9 (69%) patients had mid zone perihilar infiltrates and 4 (31%) had lower zone infiltrates. In patients with bacterial pneumonia, 2 had mid zone infiltrates and one had evidence of right upper lobe fibrosis with secondary pneumonia.

CD4 count

The mean CD4 count was 85.1 cells/μL (48 subjects). The mean CD4 count in patients diagnosed to have TB was 88.3 cells/μL (32 subjects). In smear positive TB, the mean CD4 count was 64.3 cells/μL (17 subjects). In smear negative TB it was 115.6 cells/μL (15 subjects). There was statistically significant difference between two groups ($P = 0.03$). The mean CD4 count in patients with PcP was 70.2 cells/μL (10 subjects). In patients diagnosed to have bacterial pneumonia, the mean CD4 count was 66 cells/μL (3 subjects).

In patients with TB, when the CD4 count was compared with the radiological picture, there was no significant difference in the different groups except in the group with miliary shadows whose mean CD4 count was relatively higher (172 cells/μL) although there was no statistical difference between the various groups.

Deaths

Six patients (10.7%) died during their course in hospital. Two were diagnosed to have smear positive TB, 3 patients had PcP, one had smear negative TB. The mean CD4 count in these patients was 46.7 cells/μL. This was significantly lower when compared to the patients who were discharged alive ($P = 0.04$).

DISCUSSION

Opportunistic infections remain the major cause of morbidity and mortality in HIV-infected individuals in India. In resource limited settings such as ours, knowledge about the prevalence of various opportunistic infections would help in making decisions regarding empirical treatment and also in prioritizing treatment for these patients.

Out of 56 patients included in this study, some of the patients already had been diagnosed to have HIV infection from elsewhere and presented with respiratory symptoms at our outpatient department. Others were diagnosed to have HIV infection while being worked up for their respiratory symptoms. The study population mostly belonged to the six districts of North Kerala to which the hospital caters. Being a tertiary care center, most of the patients with milder symptoms would have obtained treatment from their local health facilities.

The mean age at presentation was 39.3 maximum number of patients belonged to the 21-40 age group (59%). 39% of the study population belonged to the age group of 41-60. The National AIDS Control Organization (NACO) also suggests that AIDS is affecting mainly young people in the sexually active group. The majority of the HIV infections (87.7%) are in the age group 15-44 years.

Males dominated the study population with a male female ratio of 3:1. The NACO figures also mention a similar ratio. In a study conducted by the dermatology department, Medical college Thiruvananthapuram, the male/female ratio was 2.3:1 and the maximum number of patients was seen in age group 21-40 (77.68%).[1]

The most common symptoms with which the subjects presented was cough (93%), followed by fever (80.7%) and dyspnea (68.4%). In two studies from North India,[2,3] the most common symptoms were fever and weight loss. However, their study population included all HIV patients irrespective of their pulmonary symptomatology. The most common symptoms in patients diagnosed to have TB were fever (92%), cough (89%), and weight loss (58%). Rupali *et al.*[4] have suggested that TB is the most common cause of prolonged fever in HIV-infected adults in India. Hira *et al.* has inferred that clinical features of HIV associated TB in decreasing order of frequency were chronic fever, chronic cough, lymphadenopathy, and hepatosplenomegaly.[5]

Nearly 66% of patients had a relapse of TB. It is a well-known fact that rate of recurrence both due to endogenous reactivation and exogenous reinfection are increased in HIV-infected patients. A HIV positive person infected with MTB has a 50-60% life time risk of developing TB disease as compared to an HIV negative person who has only a 10% risk. This is especially important in India where it estimated that 40% of the adult population harbors MTB. Furthermore, HIV-infected persons who become newly infected with MTB rapidly progress to active TB disease.

Lymphadenopathy (73%) and candidiasis (72%) were the most common physical findings. TB could be proved from 4 cases of cervical lymphadenopathy. Hepatosplenomegaly was detected in 12 subjects. In a study from Thiruvanathapuram,[7] candidiasis was detected in exactly 72% of the cases whereas in 2 studies from North India, the figures are much less (40.3% and 39.3%).

Anemia was detected in 48% of the patients. This is similar to the figure of 50.5% suggested by Sharma *et al.*

TB was the most common cause for respiratory symptoms in this study group. In India, most of the studies find that TB is the most common opportunistic pulmonary infection

although many suggest that extrapulmonary TB may be more common than pulmonary TB. TB accounted for the symptoms of 63% of the patients. Comparing with other studies, Sharma *et al.* - 71%,[2] Sircar *et al.* - 54.8,[3] Rajendran and Devasia - 37.8%,[7] Kumarasamy *et al.* - 49%,[9] Chacko *et al.* - 52%.[10] But in all these studies, both pulmonary and extrapulmonary TB were included and the study population consisted of all HIV, irrespective of their symptoms unlike our study where only patients with respiratory symptoms were evaluated. Both smear positive and smear negative TB were evaluated. Both smear positive and smear negative TB were equally identified in our study population (50% each). The NACO guidelines for HIV TB suggest that TB is harder to diagnose in HIV-infected people than in those not infected with HIV. In late HIV, 35-50% of HIV positive people are detected to have pulmonary TB on sputum sample examination, which means that the *Mycobacterium* may not be detected in the sputum in large numbers of TB patients with late stage HIV.

PcP was diagnosed in 23% of the patients. The cysts of *Pneumocystis jirovecii* were visualized in only two patients. The rest of the patients were diagnosed based on their clinical and radiological features and their response to treatment. The presence of PcP in other related studies are Kumarasamy *et al.* - 6%, Rajendran and Devasia - 1.8%, Sharma *et al.* - 7.4%, and Rupali *et al.* - 7%. Bacteria could be isolated from the sputum in only three patients (5%) in our study. In other studies, Chacko *et al.* - 44%, Nair *et al.* - 13.2%, Rajendran and Devasia - 2.3%, the occurrence of bacterial pneumonia has been variable. This might be due to the variation in the facilities available at these centers. The low occurrence of PcP might be due to the fact that in the above mentioned related studies, all systems were included unlike ours where only patients with respiratory symptoms were included. More recent reports have noted that PcP comprises a significantly greater percentage of cases of pneumonia than it did in the past. This trend dramatically contrasts with that observed in industrialized nations, where a reduction in the number of cases of PcP has occurred as a result of the widespread use of primary *P. jirovecii* prophylaxis and HAART. Throughout the developing world, the rate of coinfection with MTB and PcP is high, ranging from 25% to 80%.[11]

No definite diagnosis could be made in 5 patients (9%). The chest radiograph was also normal in these patients. The reason could be that they could be not diagnosed because of nonavailability of further investigations. Another possibility is that in patients with HIV infections, symptoms and pulmonary function test abnormalities may arise even before or independent of overt pulmonary complications. This may be reflecting a heightened susceptibility of these patients to the effects of cigarette smoking.(Table 1)[12]

The mean CD4 count in this study was 85.1/μL. 95.6% of the patients had a CD4 count <200 cells/μL. In the study by Sharma *et al.*, this accounted for 82.6% of the patients. In patients with TB, the mean CD4 count was 88.3 cells/μL (Table 2). The CD4 counts of smear positive TB were significantly lower than that of smear negative TB patients ($P = 0.03$). This is supported by a study by Jones *et al.* where acid fast smears were more often positive in patients with low CD4 cell counts.[13] The CD4 count was also very low in patients with miliary TB. The mean CD4 count in patients with bacterial pneumonia and PcP were >80 cells/μL in our study. Ramalingam suggests that the mean CD4 count among normal South Indians is significantly lower than that in western population and parallels that of the Chinese.[14] This may be the reason for the lower CD4 counts in our study population.

In spite of the low CD4 count, most patients with smear positive TB presented with classical upper zone shadows (44%). Most of the patients with smear negative TB had hilar shadows or pleural effusion (56%) (Table 2). Again contrary to the usual findings, the patients with hilar prominence had a relatively high CD4 count* (172 cells/μL). Pleural effusion was seen in both smear positive and negative TB patients over wide range of CD4 counts. Upper zone infiltrate typical of PTB reactivation is usually associated with early HIV infection and so seen at higher CD4 counts. Lower or midzone infiltrates, adenopathy, interstitial pattern or normal radiograph are associated with advanced HIV disease and so at a lower CD4 count[15] (Table 3). The large discrepancy seen in this study could be due to the fact that CD4 counts in some of the patients were evaluated months after they had been diagnosed to have TB and started on treatment. We believe that exceptionally high

Table 1: CXR distribution in tuberculosis

CXR distribution	Smear positive	Smear negative	Total
Upper zone	8	1	9
Mid zone	3	2	5
Lower zone	2	4	6
Hilum	0	5	5
Pleural effusion	3	5	8
Hydropneumothorax	1	0	1
Miliary	1	1	2
Total	18	18	36

CXR: Chest X-ray

Table 2: Relation between CD4 count in smear positive and smear negative TB

TB cases	Number	Mean CD4 count (cells/μL)
Smear positive	18	64.3
Smear negative	18	115.6

TB: Tuberculosis

Table 3: Relation between CD4 count and CXR distribution in smear positive and smear negative TB

CXR distribution	Smear positive	Average CD4 count (*n*)	Smear negative	Average CD4 count (*n*)
Upper zone	8	59.1 (6)	1	98 (1)
Mid zone	3	71 (3)	2	39 (1)
Lower zone	2	96.5 (3)	4	101 (4)
Hilum	0	-	5	172 (5)
Pleural effusion	3	60.6 (3)	5	93.3 (3)
Hydropneumothorax	1	70 (1)	0	-
Miliary	1	21 (1)	1	25 (1)
Total	18	64.3 (17)	18	115.6 (15)

CXR: Chest X-ray, TB: Tuberculosis

CD4 count is due to the improvement in counts with anti TB treatment.

Patients diagnosed to have PcP mostly has bilateral mid zone infiltrates (69%). In patients diagnosed to have bacterial pneumonia, pneumococci were isolated in two patients and *Klebsiella* species in one. In literature too, *Streptococcus pneumoniae* is responsible for the majority of bacterial pneumonias in HIV-infected patients.

Six patients (10.7%) died during their course in the hospital. They had very low CD4 count compared to those who were discharged (46.7 cells/μL) ($P = 0.004$). In the study by Sharma *et al*., 21 patients (15.6%) died in hospital, most of them due to TB (16 patients) and PcP (4 patients). All patients who died in hospital except for one, had CD4 count <200 cells/μL.

The pulmonary manifestations detected in this study may be very low compared to the actual prevalence of these complications. In a study by Wallace and Hannah at autopsy, all patients with HIV infection had pulmonary disease. Only one third of the diagnoses had been made when the patient was alive.[16]

CONCLUSION

The most common cause for respiratory symptoms in HIV-infected individuals was pulmonary TB (63%). The other opportunistic infections in the study group were PcP (23%) and bacterial pneumonia (5%). The mean CD4 count in patients with smear positive TB was significantly lower than that of smear negative TB in these patients. No definite radiological pattern could be predicted for patients with TB according to their CD4 count. The patients who died in the hospital (10.7%) had a significantly low CD4 count.

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