Original Research Article

The clinical profile of patients diagnosed as having HIV infection with special reference to Joint manifestations and its correlation with CD4 count.

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Abstract

Introduction: India has the world's third largest population suffering from Human Immuno deficiency virus(HIV) infectionV.HIV has many rheumatic manifestations and there is scarcity of studies exploring the spectrum of rheumatic manifestations in our population.**Objectives:** To study the prevalence and clinical profile of patients with HIV and to study the spectrum of Rheumatic manifestation in HIV and to determine any correlation with CD4 count.**Study design**: Descriptive study.**Place and duration of study**: Patients attending antiretroviral (ART) clinic of Government Medical College hospital, Thiruvananthapuram.**Methodology**: A structured questionnaire was given to 79 confirmed cases of HIV infection.The data was analyzed and the prevalence of rheumatic manifestations was determined.CD4 count was tested for any correlation with rheumatic manifestation or any of the other variables.**Results and Discussion**:The major mode of transmission was heterosexual ie in 94.9%.There was one case of reactive arthritis, one of fibromyalgia and 5 cases of HIV associated arthralgia.Rheumatic manifestations were seen in 8.9% of the study group.89.9%of the patients were on antiretroviral therapy and 45.6% reported improvement with treatment.CRP was positive in 10%,RA factor in 10% and ANA in 5.1%.46.8% patients had CD4 count less than 200,39.2% between 200-500 and 13.9% more than 500.The comparison between CD4 in different stages showed a significant difference(p-0.00).The mean CD4 of patients without rheumatic manifestations was 274.4cells/cubic millimeter and 263.7 cells/cubic millimeter in the presence of rheumatic manifestation. Opportunistic infections was seen in 43%.The mean CD4 count in patients without opportunistic infections was 364.**Conclusion**: Spondyloarthropathy one of the common rheumatic manifestations is not seen in the studied group. There was no statistical difference between CD4 count in HIV patients with and without rheumatic manifestation. The majority of the patients (90%) were on antiretroviral therapy which indicates the acceptability of treatment. Opportunistic infection was not seen in 57% patients suggesting the effectiveness and good adherence to ART.

Keywords: HIV, Joint manifestations; CD4 count; Spondyloarthropathy, Reactive arthritis; Fibromyalgia; Opportunistic infections.

Introduction

India is home to the world's third largest population suffering from HIV.There is 34 million people living with HIV globally ,in India it is 2.4 million(0.36%) and in Kerala around 25,000(0.12%). From a disease initially restricted to the homosexuals, intravenous drug abusers and hemophiliacs now the disease has turned into a global pandemic. There has been a report of many immunological and rheumatic manifestations in HIV infection. The estimates of the prevalence of rheumatic manifestations in HIV infection differ widely.These diseases can be those which are unique to HIV infection like diffuse infiltrative lymphocytosis syndrome, or found in HIV infected patients similar to non-infected individuals (Reiter's syndrome,psoriatic arthritis, etc.) and some conditions like rheumatoid arthritis or SLE which is observed to be usually ameliorated by HIV infection .

Reiter syndrome and reactive arthritis represent the most common arthritides encountered in HIV infection. The frequency of Reiter syndrome,which is the first reported rheumatic manifestation in HIV is 100 to 200 times higher in HIV-infected patients than in noninfected patients, with an overall prevalence of 5% to 10%[1]. Arthritis,conjunctivitis and urethritis are the classic triad of Reiter syndrome.Most of the patients have a benign self limiting course while some have severe course with poor response to drugs. In HIV infected people psoriatic arthritis occur at a rate of 10 to 40 times higher than in the general population, and the overall prevalence is about 2% to 3%. Patients with HIV infection and psoriatic arthritis can either have an articular disease that is sustained and aggressive or just a mild and intermittent joint involvement.HIV-associated arthritis has an overall male preponderance and manifests as a non-erosive oligoarthritis of the lower extremities without enthesopathy, mucocutaneous involvement and HLA-B27 gene expression. It is self-limited, usually lasting a few weeks to 6 months. Diffuse infiltrative lymphocytic syndrome (DILS) is a condition unique to HIV.The diagnostic criteria is HIV seropositivity with bilateral

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salivary gland enlargement and xerostomia for more than 6 months with histological confirmation of salivary or lacrimal gland lymphocytic infiltration in the absence of granulomatous or neoplastic enlargement. Some HIV-infected patients fail to develop the entire spectrum of clinical manifestations for disease to be called as ankylosing spondylitis, Reiter's syndrome, or psoriatic arthritis, and are labelled as undifferentiated spondyloarthopathy.Studies from Thailand and sub-Saharan Africa have shown an association of HIV infection with reactive arthritis and other spondyloarthropathies. Incidence of spondyloarthropathy in patients with HIV infection has been reported, ranging from 0.2-38%. Berman et al reported a prevalence rate of 9.9%for Reiter's syndrome and 1.9% for psoriatic arthritis[2].Louthrenoo reported an incidence rate of 8% for Reiter's syndrome, 9% for psoriatic arthritis, and 38% for undifferentiated spondyloarthropathy[3].Vasculitis,HIV associated arthralgia,HIV associated arthritis,septic arthritis are some of the other rheumatic manifestations in HIV.Many of these conditions are benign and self-limited, others are not. Articular conditions are either caused by the HIV infection itself, triggered by adaptive changes in the immune system,or secondary to microbial infections.The prevalence of inflammatory musculoskeletal manifestations remain uncertain but these disorders cause a significant decrease in the patient's quality of life. Given the longevity achieved with current prophylactic and therapeutic strategies, quality of life has emerged as a significant medical outcome.

Materials and Methods

A Descriptive study was conducted among the confirmed cases of HIV infection attending ART clinic of government medical college hospital,Thiruvananthapuram.A Confirmed case of HIV defined as a patient with a positive result from an initial HIV antibody test and subsequently confirmed by positive result from a supplemental HIV test different from the initial test and was classified according to the WHO clinical staging of HIV/AIDS.The diagnosis of spondylo-arthropathy defined by the European spondyloarthropathy study group(ESSG) classification criteria for spondyloarthropathy. Reactive arthritis defined as the presence of rheumatoid factor negative peripheral arthritis in at least one joint associated with clinical or microbiological evidence of a causative extaarticular infection Reiter's syndrome is a special form of reactive arthritis and characterized by the combination of arthritis,redness of eyes and urinary tract signs Psoriatic arthritis defined by classification criteria for psoriatic arthritis(CASPAR). Undifferentiated spondylo-arthropathy was defined as arthritis in adults which fulfilled the ESSG criteria but did not meet the criteria for established disease categories like ankylosing spondylitis, psoriatic arthritis,reactive arthritis. Rheumatoid arthritis defined by 2010 ACR-EULAR classification criteria.Fibromyalgia and other connective tissue disorders classified according to established American college of rheumatology criteria.The patient were included in the study after getting a written informed consent.The sample size was calculated to be 79 and data was collected using a structured questionnaire.A detailed history will be taken from patient regarding age,sex ,education,mode of acquiring the HIV infection , underlying disease symptoms.All symptoms and signs of the musculoskeletal system and other related abnormalities are gathered.The details of the stage at diagnosis,CD4 count at diagnosis,present stage any opportunistic infection will be gathered from the treatment records.A detailed clinical examination with special emphasis on musculoskeletal system is to be done. The following laboratory investigations are to be carried out- serum CD4 lymphocyte count,routine blood examination,erythrocyte sediment-ation rate,C reactive protein ,Rheumatoid factor,ANA,serum uric acid.renal function test,liver function test and relevant imaging study as indicated clinically.Categorical variables will be expressed as proportions and quantitative variables as mean and standard deviation.Analysis of data will be done using appropriate statistical techniques using SPSS(Statistical package for the social sciences). The values of probability(p) will be determined.Differences will be considered significant when $p<0.05$.

Results and Discussion

We studied 79 patients over a period of one year.The mean age of study population was 43.6. The major mode of acquiring the illness is heterosexual ie in 94.9%. About 21.5% of the study group was asymptomatic at presentationGiri et al observed that 67.8%patients were asymptomatic and detected by routine screening(4).The percentage of patients with fever was 24.1,weight loss 16.5,diarrhoea 6.3,lymph node enlargement 7.6,oral ulcers 6.3,cough 6.3,dyspnea 2.5,fatigue 1.3 and skin disease in 1.3. In the study ,35.4% patients were in stage 1,21.5% were in stage 2,22.8% in stage 3 and 20.3% were in stage 4. 81% patients were in stage 1 at the time of interview .Of the rest,10.1% were in stage 2,3.8% in stage 3 and 5.1% in stage 4. In the study 92.4% patients had no rheumatic manifestation and 7.6% had rheumatic manifestations.(figure 1)

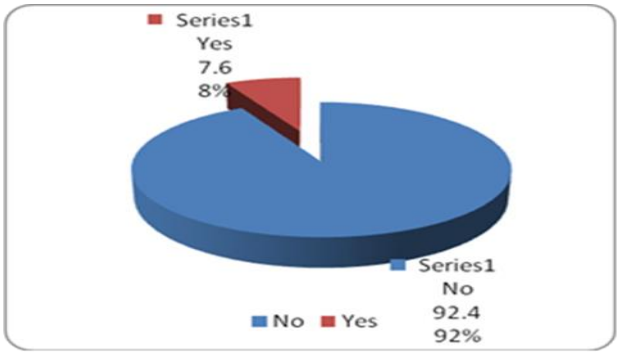

Fig 1:Distribution of rheumatic manifestation

In the study rheumatic manifestations were seen in seven patients,one patient with reactive arthritis,one with fibromyalgia and five patients with HIV associated arthralgia. The patient with reactive arthritis is a male of age less than 30 who was at stage 3 of HIV infection.The CD4 was less than 200 at diagnosis. Prevalence of reactive arthritis in studies varies between 0-11%(5,6) The patient with fibromyalgia was a female of age between 40-50.The stage at diagnosis was stage 4 and the CD4 count was between 200-500.The distribution of selected variables in patients with hiv associated arthralgia is given in table 1.About 89.9% of patients were on ART and the distribution of selected variables based on art given in table 1.

Table 1:Distribution of selected variables based on ART

		Count	Percent
Initiated on ART	No	8	10.1
	Yes	71	89.9
Drugs being used	Not on drugs	9	11.4
	TLE(Tenofovir,lamivudine,efavirenz)	60	75.9
	ZLN(Zidovudine,lamivudine,nevirapine)	10	12.7
Any change of symptoms with treatment	No change	33	41.8
	Worsened	2	2.5
	Improved	36	45.6
	Not applicable/Not on treatment	8	10.1
Any joint symptoms after ART	No	71	89.9
	Not on ART/Not applicable	8	10.1

In our study at diagnosis 46.8% patients had CD4 count less than 200,39.2% patients had CD4 count between 200-500,13.9% had CD4 count more than 500(table 3). The mean CD4 count at diagnosis in stage 1 is 371.6 ,stage 2 is 370.8,stage 3is 156.9 and stage 4 is 130.1. The comparison between the CD4 count in the different stages using ANOVA test showed a significant difference(p-0.000) implying that the CD4 count in each stage is different from the other(figure 2). The mean CD4 count at present in stage is 540.3 , stage 2 is 347.3,stage 3 is 191.3 and stage 4 is 57.8. 1The comparison between the CD4 count in the different stages using ANOVA test showed a significant difference(p-0.001).

Table 2: Distribution according to CD4 at time of diagnosis

CD4 at the time of diagnosis	Count	Percent
<200	37	46.8
200 – 500	31	39.2
>500	11	13.9

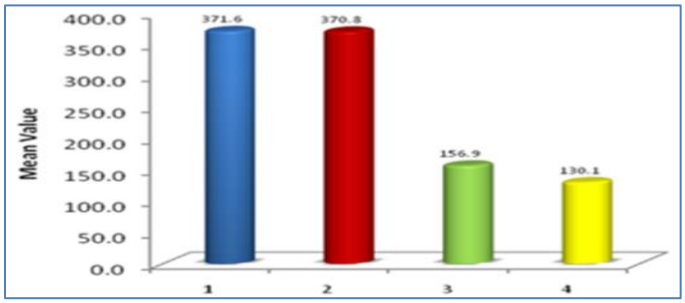

Fig 2:Comparison of CD4 at the time of diagnosis with stage at diagnosis

Opportunistic infections were seen in 43%of patients in our study,oral candidiasis and extrapulmonary tuberculosis being the most common(figure 3). The mean CD4 count of patients without opportunistic infections was 364.The lowest mean CD4 OF 55.7 was seen in CMV retinitis.The descriptive statistics for cd4 at time of diagnosis in patients with opportunistic infection is given in table 4.

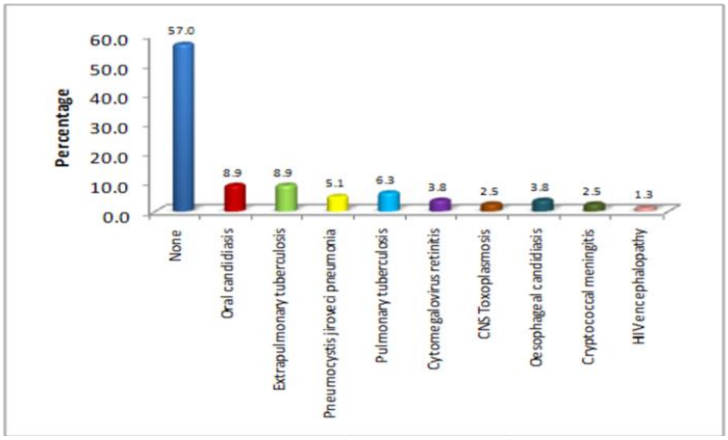

Fig 3: Distribution of Opportunistic Infections

Table 3: Descriptive Statistics for CD4 at time of diagnosis in patients with opportunistic infection

Opportunistic infections	Mean	SD	Median	Minimum	Maximum
None	364.0	195.7	332.0	47.0	777.0
Oral candidiasis	136.3	74.6	157.0	32.0	211.0
Extrapulmonary tuberculosis	175.1	130.9	120.0	38.0	394.0
Pneumocystis jiroveci pneumonia	116.0	131.8	66.0	24.0	308.0
Pulmonary tuberculosis	93.0	41.6	79.0	54.0	159.0
Cytomegalovirus retinitis	55.7	16.3	59.0	38.0	70.0
CNS Toxoplasmosis	434.0	560.0	434.0	38.0	830.0
Oesophageal candidiasis	296.7	116.8	333.0	166.0	391.0
Cryptococcal meningitis	59.5	57.3	59.5	19.0	100.0
HIV encephalopathy	80.0	0.0	80.0	80.0	80.0

In the study correlation between CD4 at diagnosis and CD4 at present was checked. The scatter diagram(figure 4) shows that no correlation was observed and a p value of 0.578 implies that there is no statistical difference between CD4 count at diagnosis and at present.

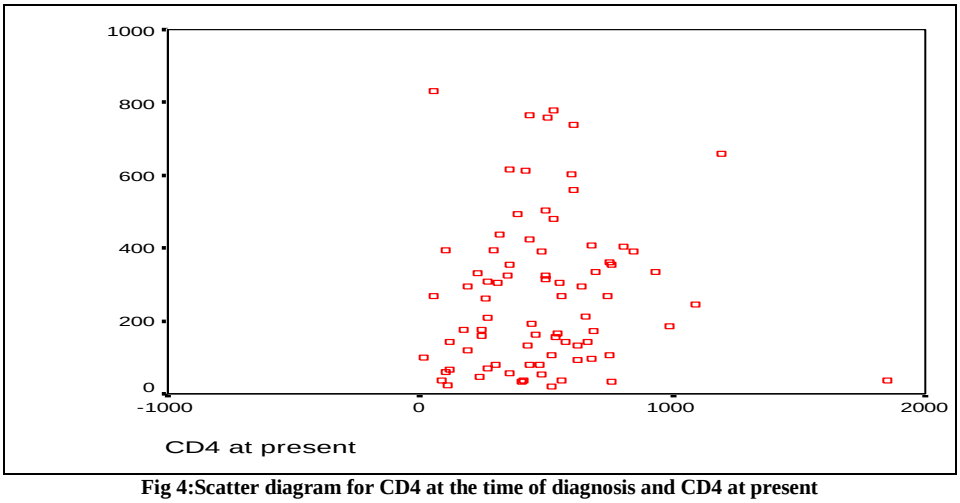

Fig 4:Scatter diagram for CD4 at the time of diagnosis and CD4 at present

The mean CD4 count of patients without rheumatic manifestations was 274.4 and those with rheumatic manifestations was 263.7. The p value is 0.904 which implies that there is no statistical difference between CD4 count in patients without rheumatic manifestations and those with rheumatic manifestations.

Discussion

The major mode of transmission was heterosexual (94.9%).Kumar et al and Nair et al have reported sexual transmission in 81.7 and 78.4%[7,8].Our study shows a higher proportion of heterosexual transmission compared to previous studies which could be due to the fact that intravenous drug abusers were excluded from the study.It also highlights the need of creating awareness about safe sexual practices in our population .In this study about 35.4% were in stage 1 at diagnosis.Though stage 1 is usually asymptomatic about 35% patients were diagnosed at this stage which is suggestive of the effective screening process in our state. The stage of the patient at the time of the study was also recorded and 81% were in stage 1.Only 5.1% patients were in stage 4.This implies the effectiveness of ART and the adherence of patients to treatment. Multiple cohort studies conducted across several continents suggest that arthralgia is common in HIV.Prevalence between 1-79% have been observed[9-11]. Krishnan et al observed that 44.8% had spondyloarthrosis ,17.2% with reactive arthritis ,HIV associated arthralgia in 17.2% and arthritis in 13.8%. The prevalence rate range of HIV associated artritisrangefrom 0.4-13[12-15].Studies by Kole et al [16] observed that the prevalence of rheumatic manifestations in HIV is 63% and Okwara et al[17]reported a prevalence of 37%. Our study gives a lower prevalence(8.9%) compared to the above studies.This could be due to the early diagnosis and the effect of antiretroviral therapy. Narayanan et al reported in his study that 50% of the rheumatic manifestations was spondyloarthropathy[18].In our study there was no case of spondyloarthropathy. In the study 89.9% of patients were on ART and 75.9% were on TLE and 12.7% were on ZLN.An improvement of symptoms with treatment was reported in 45.6% and 41.5% did not experience any change with treatment. Our study indicate that there is a better acceptance of ART in our society which could be due to better educational status of our population. CNS toxoplasmosis showed a high mean CD4 count of 434 cells/cubic mm in our study.This high CD4 count observed was due to the fact that out of two patients with toxoplasmosis one had a CD4 count of 38 cells/cubic mm and the other patient had a CD4 count of 830 cells/cubic mm.This had shifted the mean to a higher value. As the number of patients were less the mean is not a very reliable representative of the CD4 count of patients with toxoplamosis and oesophageal candidiasis. The comparison between the CD4 count in the different stages using ANOVA test showed a significant difference(p-0.000) implying that the CD4 count in each stage is different from the other.It was observed that there is a reduction in CD4 count as the stage advances. there is no statistical difference between CD4 count in patients without rheumatic manifestations and those with rheumatic manifestations studies.

Cascado et al[19]determined the musculoskeletal manifestations in HIV infection and its correlation with CD4 count,He observed that osteoarticular infections can occur when CD4 is less than 100 cells/cubic mm.Zhang et al[20]observed that CD4 depletion may predispose to rheumatic manifestations.This is in contrary to our

finding that rheumatic manifestations had no correlation with CD4 count.

Conclusion

Rheumatic manifestations were less in our people(8.9%) and spondyloarthropathy one of the major rheumatic condition commonly seen in HIV was not seen in our group. There was no statistical difference observed between CD4 count in patients with and without rheumatic manifestations (p-0.904)

Limitations of Study

The study was done in a small sample of patients (79) . Another factor is that though there is an equal proportion of patients in each stage at the time of diagnosis, about 81% patients were in stage 1 at the time of interview .This could be a reason for the low prevalence of rheumatic manifestations.

Consent

Informed written consent taken

Ethical Approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Abbreviations

ANA-Antinuclear antibody
ART-Antiretroviral therapy
CD4-Cluster of differentiation 4
CRP-C reactive protein
ESR-Erythrocyte sedimentation rate
HAART-Highly active antiretroviral therapy
HLA-Human Leucocyte antigen
HIV-Human immunodeficiency virus
RA-Rheumatoid factor
SLE-Systemic lupus erythematosus
TLE-Tenofovir, Lamivudine,Efavirenz
ZLN-Zidovudine, Lamivudine, Nevirapine

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