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Rheumatological Manifestations in Patients Infected with HIV - A Clinical Study

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ABSTRACT

Aims and Objectives

To study rheumatological manifestations in patients infected with HIV with regards to prevalence, pattern of involvement, correlation of various types of rheumatological syndromes with the grades of HIV infection and pattern of laboratory investigations

Method:

This study was conducted over a period of 6 months at Sassoon general hospital, Pune. A total of 100 HIV patients presenting with rheumatological complaints were enrolled in this study and analysed regarding clinical, laboratory and radiological features and disease activity score 28 was calculated.

Results:

There were 68 males and 32 females and Male to female ratio was 2.1:1. 78 % cases were in age group of 20 to 50 yrs that was sexually active group. A total of 75 % patients were in HIV stage 3 and 4 indicating high incidence of rheumatic manifestations with progression of HIV disease. The mean CD4 count was 264 mm3 and 62 % patient had CD4 between 200 to 499 mm3.The commonest rheumatic manifestation found was arthralgia (45%), while other common manifestations found in decreasing frequency were Arthritis (17%), myopathy (10%), spondyloarthropathy (9%), vasculitis (8%), painful articular syndrome (2%), Reiter's arthritis (3%), psoriatic arthritis (2%), septic arthritis (2%) and rheumatoid arthritis (2%) cases. A raised ESR was seen in 81 % patients and raised CRP in 78% patients. Commonest radiological abnormality seen was soft tissue swelling and erosive changes of articular surface (11.1%). Arthritis due to varying aetiology in HIV patient usually has moderate disease activity as per DAS 28 ESR score hence it is less noticed by physicians.

Conclusion:

Physician should look for rheumatological manifestations in HIV, distinguish them from classic rheumatic diseases and do timely intervention to prevent disability and deformity and to improve the quality of life.

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KEYWORDS: *HIV, Rheumatological condition, clinical study*

Background

HIV infection is a pandemic which is reported to have many immunological and rheumatic manifestations. Patients with HIV now live longer as a result of more effective and available treatments therefore the challenges of HIV-associated rheumatic manifestations are growing. Incidence of rheumatic manifestations in pre HAART era were 10 to 30 % and in HAART era is 2 to 7 %. Nearly all rheumatic conditions have been reported in HIV patients in various scientific publications. Certain diseases seem to be particular to HIV infection (i.e. HIV-associated arthritis, DILS, HIV-associated polymyositis). Other diseases, specifically CD4-mediated diseases such as RA and SLE, tend to go into remission with disease

activity and tend to flare with HAART. (3) (5)Immunological and rheumatological disorders may range from direct effect of the virus, opportunistic infections, excessive immediate-type hypersensitivity reactions to antiretroviral therapy, exaggerated immune response to existing opportunistic infections known as immune reactivation syndrome and to increased incidence of reactive arthritis. (4). HAART has resulted in certain diseases (i.e., DILS, late opportunistic infections) decreasing in prevalence but also is associated with new side effects (e.g., osteonecrosis, myopathy, rhabdomyolysis). With IRIS after HAART, a new spectrum of autoimmune and autoinflammatory disease has emerged requiring special attention.

MATERIAL & METHODS

First 100 cases were selected from Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital,Pune ART clinic and wards who presented with rheumatological manifestation. HIV infected patients who came between December 2013 to May 2014 were included in study. HIV Positive with age more than 14 years who were on HAART or not on HAART were included in study while patients less than 14 years of age, past history of trauma to joint, diabetes, hypothyroidism, haemophilia or family history of rheumatological disease were excluded. Study protocol was presented to the institutional ethics committee and clearance was taken. A descriptive observational study was performed. A written informed consent was taken from every selected case. Once the patient was selected, a detailed history with respect to their demographic features and general, systemic and musculoskeletal examination was done according to a standardised proforma with due importance to the HIV disease, symptomatology, clinical presentation, investigations and treatment of all the patients. Laboratory investigations done were test for Human immunodeficiency virus (HIV), CD4 count, Erythrocyte sedimentation rate (ESR), Anti nuclear antibodies, Anti-CCP, VDRL, HbsAg, RA factor, CRP, Synovial fluid study. Radiological investigations done were X-ray, USG and MRI of involved joints. All the clinical findings of the patients were assessed. These were correlated with the laboratory investigation and radiological investigations. Final diagnosis was reached by taking into consideration all the above findings. In all patients included in study who had arthritis of any form, DAS 28 ESR was calculated.

Results:

In the present study, 68 were male and 32 were female. 78 % cases were in age group of 20 to 50 yrs that was sexually active group. A total of 75 % patients were in HIV stage 3 and 4 indicating high incidence of rheumatic manifestations with progression of HIV disease. The mean CD4 count was 264 mm3 and 62 % patient had CD4 between 200 to 499 mm3.Joint pain was the commonest presenting symptom, found in 45 % cases, followed by this, joint pain with joint swelling was found in 17 % cases. Other symptoms in decreasing orders were backache, muscle pain and generalized muscle wasting. The commonest rheumatic manifestation found was arthralgia in 45 %, while other common manifestations found in decreasing frequency were Arthritis in 17 %, myopathy in 10 %, spondyloarthropathy in 9 %, vasculitis in 8 %, painful articular syndrome in 2 %, Reiter's arthritis in 3 %, psoriatic arthritis in 2% septic arthritis in 2 % and rheumatoid arthritis in 2 % cases. Arthralgia and HIV associated arthritis both were predominantly oligoarticular and most commonly affected knee joint with majority of patients in stage III of HIV disease .HIV infection associated myopathy was seen in 10 % cases, with myalgia seen in 5 % patients, HIV wasting syndrome in 3 % and drug induced myalgia in 2 % patients due to drugs zidovudine and statin respectively. Painful articular syndrome was found in 2 % cases infected with HIV with mean duration of 12 hours. 9% cases had spondyloarthropathy out of which 2 cases were ankylosing spondylitis and 7 cases were undifferentiated spondyloarthropathy. Majority of these cases were not on HAART. Reactive and psoriatic arthritis was seen in 2 % cases each.8% patients had vasculitis among which majority were females. All patients had very low CD4 counts showing incidence of HIV vasculitis in young population and in end stage of HIV disease .RA was seen 2% patients with gradual onset of symmetrical disease which was polyarticular in nature with predominant involving small joints of hands. Both patients were on HAART. Female patients had deformity inspite of HAART and a CD4 count of 354 mm3. In this study, raised ESR was seen in 81 % patients and raised CRP in 78% patients. CRP is more specific than ESR in HIV patients. Commonest radiological abnormality seen was soft tissue swelling and erosive changes of articular surface (11.1%). Periarticular osteoporosis was noted in 9% of cases, reduced joint space in 7% of cases and sacroilitis was noted in 5 % of cases. Arthritis due to varying etiology in HIV patient usually has moderate disease activity as per DAS 28 ESR score hence it is less noticed by physicians.

DISCUSSION

The maximum number of HIV positive male and female in 20-50 years age group indicate high risk

among the sexually active population. 75 % patients were in HIV stage 3 and 4 indicating high incidence of rheumatic manifestations with progression of HIV disease.

This study showed the commonest rheumatological manifestations seen in HIV infected patients were arthralgia, myalgia and HIV associated arthritis, while vasculitis is also one of the common rheumatic manifestation encountered in this population.

Arthralgia was predominantly intermittent (86.6 %), oligoarticular (51.1%) and involved most commonly knee (66.6%), shoulder, elbow and ankle joints. Majority of these patients were in stage II and stage III of HIV disease.

HIV infection associated arthritis; an inflammatory articular syndrome was present in 17 (17%) cases. It was predominantly oligoarticular (58.8%); asymmetric (70%) and involved most commonly knee joint (70%) and majority of patients (64.7 %) who had arthritis in this study were in stage III of HIV disease. The mean duration of arthritis noted was 38 days in this study.

In the present study, myopathy was found in 10 % patients with HIV.HIV infection associated myalgia was seen in 5 (50 %) patients, HIV wasting syndrome was seen in 3 (30 %) patients and drug induced myalgia in 2 (20 %) patients due to drugs zidovudine and Atorvastatin respectively. Myalgia was generalized in 5 (50 %) cases and localized in 2 (20 %) cases.

Painful articular syndrome was found in 2 (2 %) cases infected with HIV. It was characteristically sharp and severe oligoarticular pain involving knee joint, intermittent nature in all affected patients with a mean duration of 12 hours. Both patients were stage III HIV disease.

In this study 9% cases had spondyloarthropathy out of which 2 cases were ankylosing spondylitis and 7 cases were undifferentiated spondyloarthropathy. Majority were young male (66%) with mean age of 30 yrs. Low backache was presenting complaint at onset of disease in 55 % patients, asymmetrical oligoarthritis in 22 % and heel enthesopathy in 22 % cases. Mean disease duration was 4.2 yr. Radiological sacroilitis was seen in 2 cases both of which were AS. Majority patients belonged to HIV stage III and were not on HAART. Undifferentiated spondyloarthropathy is the commonest subtype followed by reactive arthritis. It has been suggested that HAART is effective in alleviation of the arthropathy by 2 mechanisms. Firstly, HIV could be prominent in joint tissues (69) and indeed the role of HAART in the patient's recovery may be related to inhibition of HIV itself at these sites (70). Secondly, the HIV inhibition might have allowed sufficient immune recovery to control a pathogen which was contributing to genitourinary or intestinal infection which was the trigger for disease.

In this study, incomplete Reiters syndrome was diagnosed in 1 of the 3 (3%) cases, 2 of them were male and 1 was female and belonged to sexually active age group. Articular manifestations, in the form of asymmetric oligoarthritis involving knees and ankles were found in both of them. Enthesopathy was seen in 2 cases and Achilles tendinitis in 1 case. Both these patients were in stage III of HIV disease.

In this study, 1 female and 1 male HIV infected patients with psoriasis was found to have psoriatic arthritis, which had developed 6 and 12 months after the diagnosis of HIV respectively.

In this study, 8% patients had vasculitis, among which 75 % were females and 25 % were male. All patients were in age group 20 to 38 yrs and had very low CD4 counts showing high incidence of HIV vasculitis in young population and in end stage of HIV disease. In 87% patients, vasculitis was localised to small or medium vessel and 13 % to large vessel. Infective etiology was seen in 37.5 % cases. In majority of cases, causative agent was not found supporting the fact that indirect effect of HIV via an immune complexes mechanism or a direct infection of vascular or perivascular tissue lead to vasculitis .HIV particles have been identified in perivascular tissue by electron microscopy or FISH. Major organ affected was CNS with hemiplegia as the most common presenting complaint. The preeminent sites are CNS, skin and skeletal muscle.

In this study, 2 male patients were found to have septic arthritis. Both patients had IVDU as a risk factor. They had arthritis, synovitis, and bursitis with tense effusion of right knee joint along with constitutional symptoms. Synovial fluid examination showed raised leukocyte counts, low glucose level and on culture Staphylococcus Aureus organism was isolated. X-ray of affected knee joint showed increased soft tissue swelling along with periosteal elevation and effusion of the joint. This patient had stage III of HIV infection. These findings suggest that IVDU is the commonest risk factor for development of HIV associated septic arthritis, as also seen in this study.

In this study, RA was seen 2 patients. They satisfied EULAR 2012 criteria for diagnosis of RA. Both were positive for RA factor and Anti-CCP. Both patients had gradual onset of symmetrical disease which was polyarticular in nature with predominant involvement

of small joints of hands. Both patients were on HAART and had CD4 count more than 300. Their mean DAS 28 ESR score was in high disease activity group. Both had RA initially in remission which had flared up after HAART. This explains the fact that initial decrease of CD4+ T cells following HIV infection and subsequent increase of pathogenic CD4+ T cells with HAART. This is in line with the view that RA is a CD4+ T lymphocyte mediated disease. A reduced disease activity of RA with HIV/AIDS on HAART may be due to protease inhibitors since they have been reported to inhibit Toll-like receptors 2 and 4, implicated in the pathogenesis of RA

In this study, the mean DAS 28 ESR score was 3.9 for seronegative spondyloarthropathy group, 4.2 for HIV associated arthritis group, 4.4 for reactive arthritis group and 4.6 for psoriatic arthritis group. All these arthritis belonged to moderate disease activity group. Rheumatoid arthritis group had a mean DAS 28 ESR score of 5.2. These patients were on HAART and had good CD4 counts. Thus it is likely that HAART exacerbated RA in these patients as RA is a CD4+ helper cells mediated disease.

Conclusion

Rheumatologists need to be aware of the wide spectrum of rheumatic diseases that occur in HIV-positive patients HAART modified the frequency and expression of some HIV related clinical syndromes and has been associated directly (toxicity) and indirectly (immune reconstitution) with the development of new ones. With longer survival and newer refinements in treatment, the spectrum of rheumatic disease seen in HIV-positive patients is very much a moving target for rheumatologists and is likely to continue to evolve.

Table 1 Rheumatic diseases occuring in patients with HIV

Unique to HIV Infection	Encountered in HIV-Infected Patients	Ameliorated by HIV Infection but Worsening or Reappearing with IRIS
Diffuse infiltrative lymphocytosis syndrome	HIV-associated reactive arthritis	Rheumatoid arthritis
HIV-associated arthritis	Polymyositis	Systemic lupus erythematosus
Zidovudine-associated myopathy	Psoriatic arthritis	
Painful articular syndrome	Polyarteritis nodosa	
	Giant cell arteritis	
	Hypersensitivity angiitis	
	Granulomatosis with polyangiitis	
	Henoch-Schönlein purpura	
	Behçet's syndrome	
	Infectious arthritis (bacterial, fungal)	

Table 2 Comparison with other Indian studies

INDIAN STUDIES				
Major Manifestation	This study	Kutty Krishnan, *et al.* (Chennai) INDIA (*N*=29) (62)	Achuthan and Uppal (Delhi) INDIA (*N*=102) (64)	Kole et al (Darjeeling) INDIA (*N*=300) (60)
Arthralgia	45 %	17.2 %	11.7 %	26.7 %
Arthritis	17 %	13.8 %	--	--
Vasculitis	8%	10.4 %	2.9 %	0.3 %
Myopathy	10%	3.4 %	--	2.0 %
SNSA	9%	24.1 %	1.96 %	0.7 %

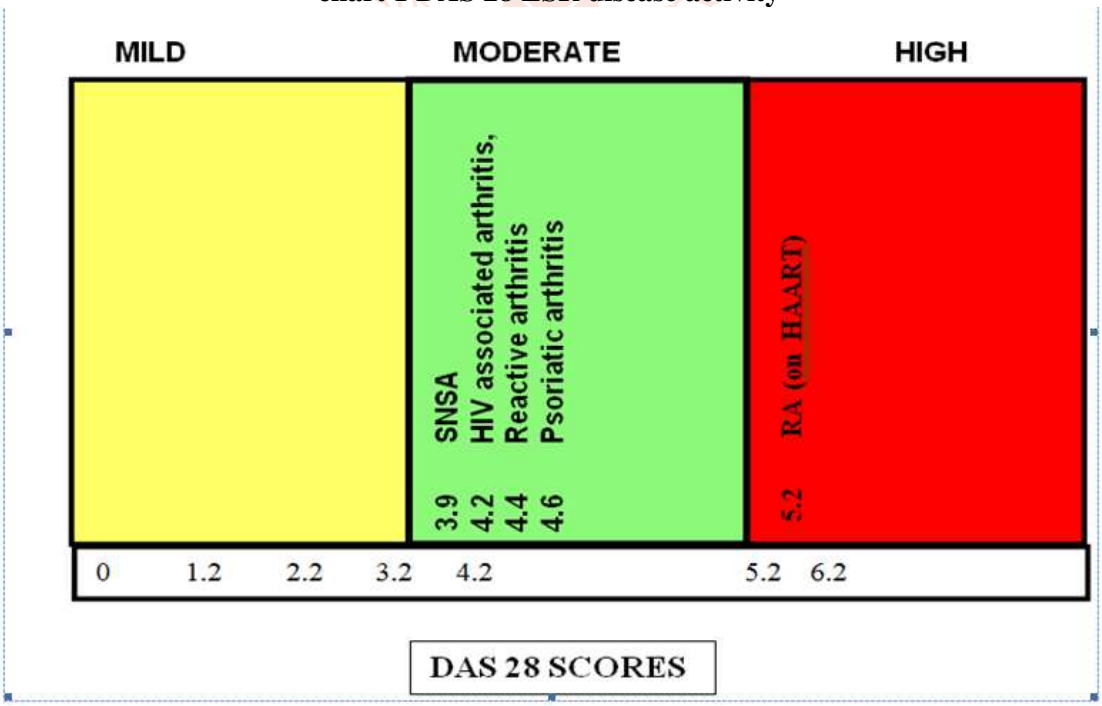
Table 3 Distribution of Rheumatic manifestation in this study

MANIFESTATION	TOTAL N=100	% OF TOTAL
ARTHRALGIA	45	45
HIV ASSOCIATED ARTHRITIS	17	17
MYOPATHY	10	10
PAINFUL ARTICULAR SYNDROME	2	2
SERONEGATIVE SPONDYLOARTHROPATHY	9	9
REACTIVE ARTHRITIS	3	3
PSORIATIC ARTHRITIS	2	2
VASCULITIS	8	8
SEPTIC ARTHRITIS	2	2
RHEUMATOID ARTHRITIS	2	2

Table 4 DAS 28 ESR score in study population

DIAGNOSIS GROUP	MEAN NO. OF TENDER JOINTS	MEAN NO. OF SWOLLEN JOINTS	MEAN ESR	MEAN VAS (mm)	MEAN DAS 28 SCORE
HIV Associated Arthritis	2	2	35	40	4.24
SNSA	3	0	32	40	3.96
Reactive Arthritis	2	2	40	50	4.48
Psoriatic Arthritis	5	4	30	30	4.62
Rheumatoid Arthritis (on HAART)	8	6	36	40	5.21
TOTAL MEAN	4	2.8	34.6	40	4.50

chart 1 DAS 28 ESR disease activity



1) Asymmetrical HIV Associated Arthritis of small joints of hand (Case no. 9 in master chart)

2) Asymmetrical reactive arthritis of knee joint (Case no. 68 in master chart)

3) Septic Arthritis of Right Knee joint (case no. 69 in master chart)

4) B/L Symmetrical HIV Associated Arthritis of Knee joints

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