

HIV Associated Arthritis

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Abstract

Objectives: To find out pattern of joints involved and effectiveness of a treatment program in HIV associated arthritis

Methods: A cohort of 26 Human Immunodeficiency Virus (HIV) associated arthritis patients (21 males and 5 females) who attended Department of Physical Medicine and Rehabilitation of the Regional Institute of Medical Sciences, Imphal was studied during 2002 and 2005. CD4 count and joint fluid examination including culture and sensitivity were performed before initiation of the treatment. A management program consisting of NSAIDs, intra-articular (I/A) methyl prednisolone injection upto a maximum of 3 times, range of mobilization exercises, strengthening of muscles around the joint, local restriction of activities to protect joints was instituted. Low dose oral corticosteroids was considered when there was persistence of joint effusion after I/A methyl prednisolone injection(s). Joint score, pain score and activities of daily living score were assessed at baseline, 3 and 6 months.

Results: Mean age of the patients was 33.2 (SD, 6.6) years. Knee joint was involved in 22 cases followed by

ankle joint in 5 cases. More than two joints were involved in 7 cases. Median CD4 count was 484 (range 231-897). The synovial fluid showed features of inflammation and was sterile. Nineteen cases (73%) remained symptom free for at least 3 months after I/A injection of methylprednisolone. Of the 7 refractory cases, all in knee joints, two had associated hyperuricemia. Synovial biopsy showed tuberculosis in one and the case responded to the addition of antitubercular drugs. And other case responded to hypouricaemic drug. Four cases responded to low dose oral corticosteroids and another case responded only after initiation of antiretroviral treatment.

Conclusions: Knee was the most commonly involved joint. Intraarticular methylprednisolone seem to be effective in the management of these cases in addition to the rehabilitation program. Low dose oral prednisolone was found to be a good adjunct in refractory cases.

Key words: Human Immunodeficiency Virus (HIV), Acquired Immunodeficiency Disease Syndrome (AIDS), Arthritis, Intra articular Methylprednisolone.

Introduction

Following the global epidemic of HIV infection, India already has the second highest number of people estimated to be living with HIV/AIDS in the world¹. In Manipur, a north eastern state of India bordering Myanmar, HIV infection is among the highly prevalent states in the country. Till February 2007², number of sero-positive cases was 25,602 with sero-positivity rate per 1000 samples screened was 136.15. Prevalence of Intravenous Drug Users (IDUs) among HIV infected persons in Manipur was as high as 72.78% in 1998 and it has come down to 19.8% in the year 2006. Whereas, the prevalence of Sexually Transmitted Diseases (STD) had shown an increasing trend from 3.9% in 1995 to 12.2% in 2005. Among antenatal women, seropositivity rate has been consistently above 1% since 1997. Presently, due to increasing life expectancy among HIV infected persons, musculo-skeletal manifestations are frequently seen¹. HIV associated arthritis³ is a separate entity which resembles subacute form of the painful articular syndrome, but joint effusion is present. It is further differentiated from reactive arthritis and Reiter's syndrome by absence of HLA-B27 and extraarticular manifestations like conjunctivitis and urethritis respectively. It is emerging as one of the important causes of arthritis in this state

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Bibliography:

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and there has been no report on HIV associated arthritis from this regional population. Therefore, this study was conducted to find out the pattern of joints involved and effectiveness of a treatment program in HIV associated arthritis.

Material and Methods

This study was conducted on 26 arthritis patients (21 males and 5 females) associated with HIV infection who attended the Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences, Imphal for treatment from the year 2002 through 2005. Written informed consent was taken from all patients for the study and interventions before taking up as a study subject. Institutional ethical committee clearance was also taken for the study. Out of 26 HIV infected patients, twenty two were referred cases from various out patient departments and clinics in Manipur and the remaining 4 patients were found HIV infected on further investigations for arthritis. Diagnosis of HIV infection was done as per National Guidelines based on three ERS (Elisa/Rapid/Simple) with different antigens or different principles⁴. Necessary pre-test counselling and informed consent were taken from the patients before doing the testing in the Voluntary, Confidential, Counselling and Testing Centre (VCCTC), Department of Microbiology, Regional Institute of Medical Sciences. Patients who had already undergone treatment with intra-articular hydrocortisone injection, having acute systemic diseases, history of conjunctivitis and urethritis, and refusal to sign informed consent were excluded from the study. Variables like age, sex, duration of HIV infection, probable mode of transmission were recorded. CD4 count and joint fluid examination for biochemical, cytological, culture and sensitivity were also carried out wherever feasible before initiation of the treatment.

A management program consisting of non steroidal anti inflammatory drugs (indomethacin was used as preferred drug), range of mobilization exercise, strengthening of muscles around the joint, local restriction of activities/life style modifications to protect joints was instituted for all patients. Intra-articular methyl prednisolone (80 mg) injection up to a maximum of three times were given to all patients who were not relieved by the initial therapy and whose CD4 count is ≥ 200 cells/mm³. Low dose oral corticosteroid was considered when there was persistence of joint effusion after intra-articular methyl prednisolone injection (s). Initiation of antiretroviral therapy (ART) was considered to those patients whose CD4 count was less than 250 cells/mm³ before intra-articular injection or oral steroid therapy. Antibiotics, hypouricaemic drugs were considered whenever applicable. Synovial biopsy was considered in refractory cases.

Joint score (number of swollen joint), pain score using visual analog scale (VAS) and activities of daily living (ADL) score using Modified Health Assessment Questioner were recorded before initiation of the treatment programme and reviewed at 3 and 6 months for every patient.

Descriptive statistics were employed analysis of the various findings.

Results

The age of patient ranged from 21 to 48 with a mean of 33.2 ± 6.6 years. The group included 9 transsexuals, 16 intravenous drug users and 1 with unknown risk factor. Duration of HIV infection ranged from 18 months to 8 years in 22 patients (mean 5 ± 1.9 years). The HIV positive on remaining 4 patients were found during investigations for arthritis. Knee joint was involved in 22 cases followed by ankle joint in 5 patients. More than 2 joints were involved in 7 cases. Median CD4 count was 484 (range 239-897).

The synovial fluid studied in 19 cases showed features of inflammation and were sterile. Seventy three percent of cases (n=19) remained symptom free for at least 3 months after intra articular injection of methylprednisolone. Intra-articular injection was repeated more than twice in 7 cases. Of the 7 refractory cases, all in knee joints, two had associated hyperuricaemia. One patient responded following addition of hypouricaemia drugs and the other to anti tubercular treatment as the case was diagnosed through synovial biopsy. Another 3 cases responded to supplementation of low dose oral corticosteroids (5-10 mg) for about 3 weeks and in one patient, oral prednisolone was continued for about 10 weeks. One case responded only after initiation of antiretroviral treatment.

Mean pain scores (VAS) before the initiation of the treatment programme, at 3 months and 6 months were 6.6 ± 0.8 , 2.3 ± 1.2 and 1.0 ± 0.9 respectively. Again, swollen joint score before the initiation of the treatment programme, at 3 months and 6 months were 1.9 ± 1.0 , 0.2 ± 0.5 and 0.08 ± 0.2 respectively. ADL score measured by using Modified Health Assessment Questionnaire at the time of admission was 13.8 ± 2.7 followed by 4.9 ± 2.5 and 2.1 ± 1.4 respectively at 3 and 6 month follow up.

Discussion

As many as 75% of HIV infected individuals will experience musculoskeletal complications which includes aseptic inflammatory or rheumatoid processes, infection, neoplasia and therapy related side effects during the course of the disease⁵. The majority of musculoskeletal manifestations of HIV disease are reactive in nature,

whether secondary to HIV infection itself or reactive to opportunistic infections elsewhere⁶. Infective causes are unusual until CD4 count drops below about 200 cells/cu mm⁷. Clinically some form of rheumatoid symptoms was seen in up to 30% of patients, with some frank inflammatory arthritis in up to 15%⁸. Unlike infective and neoplastic pathologies occurring in HIV infection, the inflammatory/rheumatic processes are seen earlier in the natural history and at higher CD4 counts, although there is a further increase in incidence associated with the development of definite AIDS or AIDS related complexes⁹. This association is a reflection of HIV immunopathy. There is renewed interest in the role of retroviruses in immune-mediated inflammatory disease. In HIV infected individuals with arthropathy, HIV antigens and DNA have been isolated from the synovium^{10,11}.

HIV associated arthritis^{12,13} occurs at least as frequently, and sometimes more commonly, than HIV indirectly associated spondyloarthropathy. It is usually presented as an oligoarthritis, predominantly affecting lower extremities, which tend to be self limiting, lasting for less than 6 weeks. Although early reports in western communities reported asymmetrical oligoarthritis as the usual pattern, polyarticular involvement is now seen frequently¹⁴. The synovial fluid leucocyte count is lower than that seen in HIV-associated reactive arthritis (500 - 2,000/l). Synovial fluid cultures are typically sterile. Isolation of HIV from one synovial fluid sample showed particles resembling retrovirus in electron microscopy. No mucocutaneous involvement is observed, and enthesopathy is also absent. The treatment, by and large, includes NSAIDs, and in more severe cases, low dose corticosteroids. Patients may respond equally well to hydroxychloroquine and sulphasalazine. Most of the patients with HIV associated arthritis are in the late stage of infection. The aetiology is still unclear, however recently both HTLV-I and -II have been suggested to induce inflammatory or autoimmune reactions which can increase significantly the incidence of arthritis.

Casado and Coworkers¹⁵ studied 74 HIV patients with osteoarticular manifestations. The study group comprised 61 men (82.4%) and 13 women (17.5%) with a mean age of 34.2 years (range 17-62). Marquez J and Coinvestigators¹⁶ also evaluated seventy-five individuals with HIV infection and musculoskeletal manifestations 65 (86%) men and 10 (14%) women. Mean age was 32 ± 4.5 years (range 21-58). Mean age is comparable with the present study (33.2 years).

The group in Marquez's study¹⁶ included 40 (53%) heterosexuals, 30 (40%) intravenous drugs users, 9 (12%) homosexuals, 3 (4%) who had received blood transfusion,

and 2 (2.6%) with unknown risk factors. Present study included 9 (34.4%) transsexuals, 16 (61.5%) intravenous drug users and 1 (3.8%) with unknown risk factor. However, Casado¹⁵ reported IV drug users as high as 70.3% (n=52). High rate of IV drug users in the present study signifies common route of transmission of HIV infection in the state Manipur.

Casado¹⁵ reported the mean CD4 of 164.7 cells/mm³ in septic arthritis, 127.1 cells/mm³ in soft tissue involvement, 245.8 cells/mm³ in spondyloarthropathies, 132.8 cells/mm³ in lymphoma, and 233.6 cells/mm³ in osteomyelitis. He suggested that CD4 counts may be useful predictors to determine the type of musculoskeletal manifestation in HIV infected persons. Median CD4 count among HIV associated arthritis in the present study was 484 cells/mm³ (range 239-897) which showed existence of the HIV associated arthritis in higher CD4 counts among HIV patients in Manipur.

A review of patients presenting at the rheumatology clinic of the Parirenyatwa Hospital, University of Zimbabwe School of Medicine by Davis P and Stein M¹⁷ revealed 14 arthritis cases with HIV infection. These 14 patients, mostly males, all had acute onset arthropathy, 5 with polyarthritis and 9 with oligoarticular diseases, usually affecting knee and ankle joints.

Stein CM and Davis P¹⁸ reported oligo/polyarticular arthritis associated with HIV infection in 26 patients (22 men, 4 women) where joints commonly involved were ankles (65%) and knees (54%), often with associated enthesitis (31%) and dactylitis (23%). They concluded that arthritis associated with HIV is most commonly characterized by oligoarticular, asymmetrical, large joint arthritis, with or without features of Reiter's syndrome, and is not associated with HLA-B27. Present study showed knee joint being involved commonly (n=22) followed by ankle joint in 5 patients. More than 2 joints were involved in 7 cases. However, a similar features like oligoarticular, asymmetric and large joint involvement was noticed in the study.

Joint fluid showed features suggestive of inflammation and cultures were sterile in the present study. Similar findings were also reported by Berman A et al²⁰ and Ntsiba H and Coworkers¹⁹. Ntsiba¹⁹ also reported microcrystals in the synovial fluids and X-ray features showing non destructive arthritis or otherwise normal study. Edward JP⁴ however expressed that the joint fluid is typically not inflammatory (<10³ cells per milliliter), though patient may respond dramatically to intraarticular steroids.

Asymptomatic hyperuricaemia is associated with ritonavir therapy, but gout has rarely been reported. Creighton S

and Co-worker²¹ recorded 18 cases of gout among 1825 HIV-positive patients, of whom 15 were receiving antiretroviral (ritonavir) therapy. Gout was seen in patients with known risk factors for gout or who were receiving ritonavir as boosted protease inhibitor and also who had lipodystrophy. Present study also featured 2 cases of hyperuricaemia but none had been treated earlier with antiretroviral therapy.

Belzunegui J and Co-investigators²², studied the characteristics of patients with the human immunodeficiency virus (HIV) and concomitant mycobacterial skeletal infection. Infections involved the knee (4 cases), spine (3 cases), hip (2 cases), elbow (1 case) and tibia (1 case). *M. tuberculosis* was the responsible organism in 9 cases, *Mycobacterium tuberculosis* plus *Staphylococcus aureus* in one case and *M. Kansaii* in one case. Patients who received specific treatments showed good results. Surgery was necessary in 4 cases. In the present study, synovectomy specimen from one patient showed tuberculosis and responded in antitubercular treatment. The spectrum of HIV-associated rheumatic disease remains a diagnostic and therapeutic challenge for the clinician²².

Human Immunodeficiency Virus has been identified in synovial fluid dendritic cells and in the synovium; immunohistochemical analysis revealed the nature of the lymphocyte infiltrate in the synovium of affected individuals. Postmortem studies suggest that there may be histologic evidence of premature aging in clinically unaffected joints from patients with acquired immunodeficiency syndrome²³.

Keat A and Rowe I²⁴ reported that conventional treatments of rheumatic lesions, including intraarticular steroids, appear to be safe and reasonably effective. Anecdotal evidence suggests that treatment with methotrexate and azathioprine leads to exacerbation of HIV disease and should be avoided.

Stein CM and Davis P¹⁸ treated all HIV patients with arthritis with a nonsteroidal anti-inflammatory drug (NSAID), most commonly indomethacin, with the addition of low-dose prednisolone (5-10 mg for 4 patients) and/or chloroquine (150 mg base daily for 11 patients) if clinically indicated. In patients in whom arthritis improved, the effect was gradual over 3-6 months.

In the present study, methylprednisolone intra-articular injection to a maximum of three times was given to all patients since all these patients remained nonresponsive to the usual conservative treatment including NSAIDs and physical modalities before attending the arthritis clinic and as initial treatment protocol for the present study. Nineteen patients (73%) got significant relief at 3 months

and 92.3% (n=24) remained symptom free at 6 months follow up. Two patients remained symptomatic even after 6 months. Our findings contradict the usual belief that HIV associated arthritis usually resolved with NSAIDs within 2-4 weeks. And intra-articular corticosteroid injection remained mainstay over and above the rehabilitation programme in the treatment of HIV associated arthritis.

Conclusion

Knee is the most commonly involved joint in HIV associated arthritis. Intra-articular methylprednisolone seems to be the mainstay in their management in the present study over and above the rehabilitation programme. Low dose oral prednisolone, hyperuricaemia drugs and antibiotics have a role in refractory cases.

References

1. Anil Mahajan, Vishal RT, S Verma. Rheumatological manifestations in HIV infection. *Journal of Indian Academy of Clinical Medicine* 2006;7(2):136-44.
2. Epidemiological Fact sheet, March 2007 issue— a quarterly publication of the Manipur Aids Control Society, Manipur.
3. Edward JP. Rheumatic disease in patients infected with Human immunodeficiency virus (AIDS). In: *Manual of Rheumatology and outpatient orthopedic disorders- Diagnosis and Therapy*. Stephen AP, Allan Gibofsky, John FB III (editors). Fourth edition. Philadelphia: Lippincott William and Wilkins; 2004: 298-306.
4. Usha KB. Laboratory diagnosis of HIV infection. In: *Diagnosis and management of HIV/AIDS – A clinician's perspective*. Usha KB, BB Rewari (editors). New Delhi: BI publications Pvt. Ltd; 2004: 126-57.
5. Berman A, Espinoza LR, Diaz JD, Aguilar JL, Rolando T, Vasey FB, et al. Rheumatic manifestations of human immunodeficiency virus infection. *Am J Med* 1988;85:59–64.
6. Buskila D, Gladman D. Musculoskeletal manifestations of infection with human immunodeficiency virus. *Rev Infect Dis* 1990;12:223–35.
7. Casado E, Olive A, Holgado S, Perez-Andres R, Romeu J, Lorenzo JC, et al. Musculoskeletal manifestations in patients positive for human immunodeficiency virus: correlation with CD4 count. *J Rheumatol* 2001;28:802–4.
8. Buskila D, Gladman DD, Langevitz P, Bookman AA, Fanning M, Salit IE. Rheumatologic manifestations of infection with human immunodeficiency virus (HIV). *Clin Exp Rheumatol* 1990;8:567–73.
9. Arnett FC, Reveille JD, Duvic M. Psoriasis and psoriatic arthritis associated with human immunodeficiency virus infection. *Rheum Dis Clin North Am* 1991;17 :59–78.
10. Espinoza LR, Aguilar JL, Espinoza CG, Berman A, Gutierrez F, Vasey FB, et al. HIV associated arthropathy: HIV antigen demonstration in the synovial membrane. *J Rheumatol* 1990;17:1195–201.
11. Hughes RA, Macatonia SE, Rowe IF, Keat AC, Knight

- SC. The detection of human immunodeficiency virus DNA in dendritic cells from the joints of patients with aseptic arthritis. *Br J Rheumatol* 1990;29:166-70.
12. Reveille JD. Rheumatic manifestations of Human Immunodeficiency Virus infection. In: Kelley's Textbook of Rheumatology . Harris ED, Budd RC, Genovese MC (editors). 7th edition. USA; Elsevier Saunders;2004:1661-75
 13. Borges NE, Samani RS, Nadkar MY. Rheumatic manifestations of HIV. In: Manual of Rheumatology. Indian Association of Rheumatology 2003:117-27.
 14. Murphy EI, Wang B, Sacher RA, Friley J, Smith JW, Nass CC, et al. Respiratory and urinary tract infections, arthritis and asthma associated with HLTV-1 and HTLV-II infection. *Emerg Infect Dis* 2004;10(1):109-16.
 15. Casado E, Olive A, Holgado S, Perez-Andres R, Romeu J, Lorenzo JC, Clotet B, Tena X. Musculoskeletal manifestations in patients positive for human immunodeficiency virus: correlation with CD4 count. *J Rheumatol* 2001 Apr;28(4):802-04
 16. Marquez J, Restrepo CS, Candia L, Berman A, Espinoza LR. Human immunodeficiency virus-associated rheumatic disorders in the HAART era. *J Rheumatol* 2004 Apr;31(4):741-6
 17. Davis P, Stein M. Human immunodeficiency virus-related connective tissue diseases: a Zimbabwean perspective. *Rheum Dis Clin North Am* 1991 Feb;17(1):89-97.
 18. Stein CM, Davis P. Arthritis associated with HIV infection in Zimbabwe. *J Rheumatol* 1996 Mar;23(3):506-11.
 19. Ntsiba H, Ngandeu-Singwe M, Makita-Bagamboula C, Yala F. Human immunodeficiency virus associated arthritis in Congo Brazzaville. *Med Mal Infect*. 2006 Dec 4; [Epub ahead of print] [Article in French]
 20. Berman A, Espinoza LR, Diaz JD et al. Rheumatic manifestation of human immunodeficiency virus infection. *Am J Med* 1988;85:59-64.
 21. Creighton S, Miller R, Edwards S, Copas A, French P. Is ritonavir boosting associated with gout? *Int J STD AIDS* 2005 May;16(5):362-64
 22. Belzunegui J, Santisteban M, Gorordo M, Barastay E, Rodriguez-Escalera C, Lopez-Dominguez L, Gonzalez C, Figueroa M. Osteoarticular mycobacterial infections in patients with the human immunodeficiency virus. *Clin Exp Rheumatol* 2004 May-Jun;22(3):343-45.
 23. Rowe IF. Arthritis in the acquired immunodeficiency syndrome and other viral infections. *Curr Opin Rheumatol* 1991 Aug;3(4):621-27.
 24. Keat A, Rowe I. Reiter's syndrome and associated arthritides. *Rheum Dis Clin North Am* 1991 Feb;17(1):25-42.