# Distinctive Rheumatic Manifestations in 98 Patients with Human Immunodeficiency Virus Infection in China

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*ABSTRACT.* ***Objective.*** To analyze the spectrum and risk factors of rheumatic manifestations in patients with human immunodeficiency virus (HIV) infection.

***Methods.*** Ninety-eight consecutive inpatients with HIV infection admitted to Peking Union Medical College Hospital from 1999 to 2006 were studied. Demographic data, routes of transmission, clinical features, and laboratory findings were collected and a database was established. Laboratory studies included blood CD3+, CD4+, CD8+, CD19+, CD16+CD3+, CD4+CD28+, CD8+CD28+, HLA-DR+CD8+, and CD8+CD38+ lymphocyte counts, and antinuclear antibody tests. Hepatitis C virus (HCV) infection was also investigated in each patient. Risk factors for the rheumatic manifestations of HIV infection were assessed by logistic regression analysis.

***Results***. Rheumatic manifestations were found in 53 (54.08%) HIV patients. Vasculitis was the most common finding (20 cases; 20.41%), including 15 cases of Behçet-like disease, 2 cases each of Henoch-Schönlein purpura and digital gangrene, and one case of central nervous system vasculitis. Other common rheumatic manifestations included Sjögren-like syndrome/diffuse infiltrative lymphocytosis syndrome (DILS; 11 cases; 11.22%), lupus-like syndrome (10 cases; 10.20%), of which 5 cases had renal involvement, and myositis (8 cases; 8.16%) including one case of zidovudine-induced myositis. No case of spondyloarthropathy was observed. Logistic regression analysis showed that Centers for Disease Control CD4+ T cell staging, erythrocyte sedimentation rate, and HCV infection were risk factors for HIV patients to develop rheumatic manifestations [p = 0.01, odds ratio (OR) = 31.80; p = 0.02, OR = 2.93; p = 0.01, OR = 17.47, respectively].

***Conclusion.*** Rheumatic disorders such as vasculitis, Sjögren-like syndrome/DILS, lupus-like syndrome, and myositis were common in Chinese patients with HIV, while articular disorders were rare. CD4+ T cell depletion and HCV coinfection may predispose patients with HIV to develop rheumatic manifestations. (First Release July 15 2007; J Rheumatol 2007;34:1760–4)

*Key Indexing Terms:*
HUMAN IMMUNODEFICIENCY VIRUS RHEUMATIC CD4 HEPATITIS C VIRUS CHINA

Human immunodeficiency virus (HIV) infection is a global health problem. Acording to the 2006 global epidemic survey on AIDS, an estimated 38.6 million people worldwide were living with HIV at the end of 2005, 4.1 million became newly infected with HIV, and 2.8 million lost their lives to acquired immune deficiency syndrome. China is one of the countries with an increasing prevalence of HIV infection. Roughly 650,000 people in China were living with HIV in 2005[1,2]. Infection by HIV is characterized by a wide array of clinical manifestations, involving multiple organ systems at late stage. Rheumatic manifestation is one of the most common features, indicative of impairment of the immunity system and connective tissue. We report rheumatic manifestations in Chinese patients with HIV and their risk factors.

## MATERIALS AND METHODS

Ninety-eight consecutive HIV-infected inpatients, who were admitted to the Department of Infectious Diseases, Peking Union Medical College (PUMC) Hospital, from December 1999 to May 2006, were included in our study. Patients received standard prophylactic regimens for opportunistic infections and specific treatments according to their infections. Seven (7.1%) had started highly active antiretroviral therapy (HAART) before they were admitted to PUMC Hospital.

Data as well as a blood sample of each patient were collected prospectively. A structured interview and a systematic rheumatological examination were also conducted for each patient by a rheumatologist (XZ or HL). Written informed consent was obtained from each patient for blood sample collection. HIV infection was diagnosed by ELISA and confirmed by Western immunoblotting. The patient's age, sex, risk factors for HIV infection, classification according to the Centers for Disease Control (CDC)[3], and clinical development of HIV infection were recorded. Laboratory studies included blood CD3+, CD4+, CD8+, CD19+, CD16+CD3+, CD4+CD28+, CD8+CD28+, HLA-DR+CD8+, and CD8+CD38+ lymphocyte counts, and

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antinuclear antibody (ANA) tests. ANA studies were by an indirect immunofluorescence test, using HEp-2 cells as substrate. Hepatitis C virus (HCV) infection was also investigated in each patient. Interferon-α therapy was initiated in all HCV-positive patients if not contraindicated.

Definitions of rheumatic disorders in HIV-infected patients are listed in Table 1.

The diagnoses of Sjögren-like syndrome/diffuse infiltrative lymphocytosis syndrome (DILS) in our cohort were all supported by histological abnormalities. However, the diagnoses of myositis in 4 cases were also made without muscle biopsy as these patients had abnormal findings on electromyography in addition to serum creatine kinase elevation. Patients with Behçet-like disease had recurrent oral and genital ulcers and skin lesions such as erythema nodosum or uveitis.

*Statistical analysis.* The Statistical Package for the Social Sciences, version 11.0 (SPSS, Chicago, IL, USA) was used to analyze data. Continuous data were summarized using means and standard deviations (SD), and compared using t tests. Categorical variables were compared using the chi-square test. The risk factors of rheumatic manifestations in patients with HIV infection were analyzed using binary logistic regression analysis. Continuous variables were recoded into categorical data by quartile or generally accepted division, as follows: erythrocyte sedimentation rate (ESR; 0–20 mm/h = 1, 21–60 mm/h = 2, 61–100 mm/h = 3, 101–140 mm/h = 4); CD4+ T cell count (1–225/$mm^3$ = 1, 226–450/$mm^3$ = 2, 451–675/$mm^3$ = 3, 676–900/$mm^3$ = 4); CD28+CD4+ T cell count (0–258/$mm^3$ = 1, 259–516/$mm^3$ = 2, 517–774/$mm^3$ = 3, 775–1032/$mm^3$ = 4); CD4/CD8 ratio (0–0.46 = 1, 0.47–0.92 = 2, 0.93–1.38 = 3, 1.39–1.84 = 4). Entry and removal probabilities for stepwise regression were 0.05 and 0.1, respectively. In all tests, all probability values were 2-sided, and p values < 0.05 were considered significant.

## RESULTS

*Spectrum and characteristics of rheumatic disorders in HIV-infected patients.* The study included 98 patients, 58 men and 40 women, aged between 6 and 73 years (median 35.9 ± 11.7 yrs). Risk factors for HIV transmission were: blood transfusion, 74 cases (74.5%); sexual transmission, 6 cases (6.1%); intravenous drug use, 2 cases (2.1%); unknown, 17 cases (17.4%). Most of these patients received contaminated blood transfusions in Henan Province, which had the highest epidemiology of HIV in China until early 1990 when mandatory testing of donated blood for HIV-1 was initiated.

The spectrum and characteristics of rheumatic disorders of our HIV-infected patients are shown in Table 2. Fifty-three patients (54.08%) had rheumatic manifestations. Vasculitis

*Table 1.* Definition of rheumatic disorders in HIV-infected patients.

| Clinical Features | Definition |
|---|---|
| Painful articular syndrome | A self-limited syndrome, usually lasting less than 24 h and accompanied by few objective clinical findings. Characterized by extremely painful bone and joint pains. Etiology is unknown. There is usually no evidence of synovitis[4,5] |
| HIV-associated arthritis | An oligoarthritis that predominantly affects knees and ankles. It lasts for < 6 wks. Synovial fluid leukocyte counts in the range of 50 to 2600 cells/$mm^3$. No association with HLA-B27. Radiographs of the affected joints are normal[5,6] |
| HIV-associated polymyositis/ dermatomyositis | Inflammatory muscle involvement proved by muscle biopsy or electromyography or creatinine kinase elevation, with and without skin involvement after the onset of the HIV pandemic. Clinical course, laboratory and electromyography findings are identical to the idiopathic except the autoantibodies described in the idiopathic forms[4,7] |
| Sjögren-like syndrome/diffuse infiltrative lymphocytosis syndrome (DILS) | Clinical features are parotid gland enlargement, xerostomia or xerophthalmia, generalized lymphadenopathy, lymphocytic interstitial pneumonitis, and meningitis as well as occasional infiltration of the gut and kidneys. Biopsy of labial salivary glands and other viscera exhibit lymphocytic infiltrates composed mostly of CD8+ cells in focal and other patterns. Other findings distinct from the idiopathic form include lack of autoantibodies such as SSA, SSB and rheumatoid factor[8-10] |
| Lupus-like syndrome | HIV-infected patients characterized by the presence of constitutional symptoms and signs, and multiple dermatological, musculoskeletal, renal, neurological, hematological, and immunological manifestations in absence of specific antinuclear antibodies such as Sm, dsDNA autoantibodies in the sera[11] |
| Vasculitis associated with HIV infection | Inflammatory vascular involvement associated with HIV infection results in highly heterogeneous clinical, pathological, laboratory, and etiological findings. Clinical spectrums have been described from localized forms such as digital gangrene to diffuse manifestations such as Henoch-Schönlein purpura, to distinct systemic necrotizing disorders such as polyarteritis nodosa, microscopic polyangiitis, and primary angiitis of the central nervous system[12,13] |
| Behçet-like disease | > 3 of the following: recurrent oral and genital ulcerations (aphthous or herpetiforme) recurring at least 3 times in one 12-mo period, eye and skin lesions special for Behçet's syndrome. Pathergy is negative[14] |

*Table 2.* Rheumatic manifestations in HIV patients. Data are percentage (cases).

| Rheumatic Manifestations | China, n = 98* | Reveille[5] US, n = 458 | Kulthanan[15] Thailand, n = 64 | Munoz[16] Spain, n = 556 | Berman[17] Argentina, n = 89 | Buskila[18] Canada, n = 52 |
|---|---|---|---|---|---|---|
| Articular features | | | | | | |
| Arthralgia | 0 | 6 | 26 | 1.6 | 22 | 40.3 |
| Painful articular syndrome | 1.02 (1) | | | | | |
| Spondylarthropathy | 0 | | | | | 15.2 |
| Ankylosing spondylitis | — | 0.5 | | | | |
| Reactive arthritis | — | | 2 | 0.5 | | |
| Reactive arthritis | — | 4 | | 0.4 | 11.2 | |
| Psoriatic arthritis | — | | | 0.4 | 1.1 | |
| Undifferentiated spondyloarthropathy | — | 7 | | 0.2 | 22 | |
| Rheumatoid arthritis | 1.02 (1) | 19 | | | | |
| HIV-associated arthritis | 1.02 (1) | 4 | 7 | 0.4 | 5 | |
| Diffuse connective tissue diseases | | | | | | |
| Muscle involvement | 9.18 (9) | | 50 | | | |
| Fibromyalgia | 1.02 (1) | 4 | | 4.5 | | |
| Polymyositis/dermatomyositis | 7.14 (7) | 2 | | | | |
| Zidovudine-induced myopathy | 1.02 (1) | | | | | 35 |
| Sjögren-like syndrome/DILS | 11.22 (11) | 1 | 10 | | 3 | |
| | 10.20 (10) | | | | | |
| Lupus-like syndrome | | 1 | | | | |
| Vasculitis | 20.41 (20) | | 18 | 0.4 | | |
| Behçet-like disease | 15.31 (15) | | | | | |
| Leucocytoclastic vasculitis | 0 | 1 | | | | |
| Henoch-Schönlein purpura | 2.04 (2) | | | | | |
| Digital gangrene | 2.04 (2) | | | | | |
| Central nervous system vasculitis | 1.02 (1) | | | | | |
| Others | 0 | | | | | |
| Septic arthritis | 0 | 1 | | | | |
| Raynaud disease | 0 | | | | | |

DILS: diffuse infiltrative lymphocytosis sydnrome.

was the most common finding (20 cases; 20.41%), including 15 cases of Behçet-like disease, 2 cases each of Henoch-Schönlein purpura and digital gangrene, and one case of central nervous system vasculitis. Other common rheumatic manifestations included Sjögren-like syndrome/DILS (11 cases; 11.22%), lupus-like syndrome (10 cases; 10.20%) of which 5 cases had renal involvement, and myositis (8 cases; 8.16%) including one case of zidovudine-induced myositis. No case of spondyloarthropathy was observed in our patients. Among 27 HCV-positive patients, 5 (18.5%) had DILS. The rate was higher than for HCV-negative HIV patients (6/71, 8.5%).

*Clinical and laboratory comparisons between the groups with and without rheumatic manifestations in HIV-infected patients (Tables 3 and 4).* By single-factor analysis, statistically significant differences were found in the variables including ESR, HCV infection, CD4+ T cell and CD28+CD4+ T cell count, CD4/CD8 ratio, and CD4+ T cell staging between the groups with and without rheumatic complications. These variables were further analyzed with stepwise logistic regression models. As shown in Table 4, the risk factors considered to affect HIV patients with rheumatic features were CD4+ T cell staging, ESR, and HCV coinfection ($p = 0.01$, OR = 31.80; $p = 0.02$, OR = 2.93; and $p = 0.01$, OR = 17.47, respectively). In our study, 7 patients had initiated HAART therapy when studied. Although there was no statistically significant difference, 71.43% (5 of 7 cases) of them had rheumatic manifestations including Behçet-like disease, Sjögren-like syndrome, DILS, polymyositis, and zidovudine-induced myopathy.

## DISCUSSION

Rheumatic manifestations could occur in HIV-infected patients with immunological abnormalities. The prevalence varied from 4% to 71.3% due to multiple factors including different races, regions and, of course, the lack of standardized reporting of the rheumatic manifestations[5,19]. The background prevalence of the common rheumatic disorders such as RA, Sjögren's syndrome, and ankylosing spondylitis is around 0.3%~0.4% each. Although China is one of the countries with an increasing prevalence of HIV infection, there have not yet been reports on the spectrum and characteristics of rheumatic complications in HIV patients in China.

In our study, HIV-infected patients with rheumatic complications were most commonly seen in stage C3 (40 of 53 cases, 75.47%) according to the CDC classification criteria[11,20,21]. Unlike information in the literature, the most commonly seen rheumatic disorders in our patients were vasculitis followed

*Table 3.* Comparation between the groups with and without rheumatic manifestations.

| | With Rheumatic Manifestations, n = 53 | Without Rheumatic Manifestations, n = 45 | p |
|---|---|---|---|
| Demographic | | | |
| Age (yrs) | 35.85 ± 11.58 | 35.89 ± 12.07 | > 0.05 |
| Sex | | | |
| Male (%) | 31 (58.49) | 27 (60.0) | > 0.05 |
| Female (%) | 22 (41.51) | 18 (40.0) | |
| Duration (yrs) | 6.45 ± 2.07 | 6.78 ± 2.62 | > 0.05 |
| Clinical categories[a] (%) | | | |
| A | 7 (13.21) | 14 (31.11) | > 0.05 |
| B | 6 (11.32) | 3 (6.67) | |
| C | 40 (75.47) | 28 (62.22) | |
| CD4+ T staging[b] | | | |
| 1 | 1 (1.89) | 3 (6.67) | 0.01 |
| 2 | 5 (9.43) | 16 (35.56) | |
| 3 | 47 (88.68) | 26 (57.78) | |
| ESR, mm/h | 55.31 ± 32.26 | 29.03 ± 27.99 | < 0.01 |
| HCV infection | 20 (37.74) | 7 (15.56) | < 0.05 |
| HAART therapy | 5 (9.43) | 2 (4.44) | > 0.05 |
| Lymphocytes (/mm$^3$) | 1107.09 ± 1001.44 | 1187.67 ± 561.08 | > 0.05 |
| CD4+ T (/mm$^3$) | 93.54 ± 160.64 | 179.38 ± 191.47 | 0.03 |
| CD8+ T (/mm$^3$) | 684.78 ± 764.43 | 663.64 ± 360.22 | > 0.05 |
| CD4/CD8 | 0.140 ± 0.22 | 0.31 ± 0.36 | < 0.01 |
| T (CD3+) (/mm$^3$) | 749.70 ± 888.74 | 902.59 ± 470.15 | > 0.05 |
| B (CD19+) (/mm$^3$) | 102.62 ± 84.95 | 108.44 ± 79.61 | > 0.05 |
| CD16+CD3+ (/mm$^3$) | 143.71 ± 127.63 | 152.44 ± 134.88 | > 0.05 |
| CD28+CD4+ (/mm$^3$) | 77.63 ± 144.30 | 193.97 ± 244.43 | < 0.01 |
| CD28+CD8+ (/mm$^3$) | 105.98 ± 89.10 | 143.62 ± 108.28 | > 0.05 |
| DR + CD8+ (/mm$^3$) | 211.98 ± 274.88 | 187.95 ± 158.52 | > 0.05 |
| CD38 + CD8+ (/mm$^3$) | 549.53 ± 585.01 | 513.74 ± 323.30 | > 0.05 |
| ANA-positive[c] (%) | 3 (5.66) | 1 (2.22) | > 0.05 |

[a,b] According to Centers for Disease Control 1993 revised classification system for human immunodeficiency virus (HIV) infection and expanded surveillance case definition for adolescents and adults[3]. [c] HEp-2 cells as substrate, indirect immunofluorescence test, ANA greater than 1:40 as positive. ESR: erythrocyte sedimentation rate; HCV: hepatitis C virus; HAART: highly active antiretroviral therapy; ANA: antinuclear antibodies.

*Table 4.* Binary logistic regression analysis of risk factors for rheumatic manifestations in patients with HIV infection.

| Variables | Coefficient | SE | Wald Chi-square | p | OR | 95% CI |
|---|---|---|---|---|---|---|
| CD4 T staging | 3.46 | 1.40 | 6.13 | 0.01 | 31.80 | 2.06~491.57 |
| ESR | 1.08 | 0.45 | 5.78 | 0.02 | 2.93 | 1.22~7.06 |
| HCV infection | 2.86 | 1.13 | 6.45 | 0.01 | 17.47 | 1.92~158.70 |

ESR: erythrocyte sedimentation rate; HCV: hepatitis C virus.

by Sjögren-like syndrome/DILS, lupus-like syndrome, and myositis, while articular disorders were rarely seen in these patients. We hypothesize that the reasons for this dramatic difference are, first, patients included in our study were inpatients with relatively severe disease, while articular disorders are more likely to occur in mild condition. Second, differences due to different regional and/or hereditary backgrounds: seronegative spondyloarthropathy was also less common in African patients with HIV who had lower rates of HLA-B27. Instead, African patients with HIV had higher expression of HLA-DR5, predisposing them to develop Sjögren-like syndrome/DILS[11]. Third and importantly, in our study, 74 cases (74.5%) obtained HIV infection by means of blood transfusion. HCV coinfection was more common in Chinese HIV patients with rheumatic complications (37.74%) than in patients without (15.56%), which may explain why vasculitis-like syndrome and Sjögren-like syndrome/DILS were the most common disorders seen in our patients.

Our study found the risk factors for HIV-infected patients who developed rheumatic manifestations included ESR, CDC staging, and HCV coinfection, reflecting inflammation, as well as disease severity, and synergistic infection might contribute to rheumatic complications. The mechanisms involved in the development of rheumatic manifestations in HIV infection included: (1) direct HIV involvement; (2) in some genetically predisposed HIV-infected individuals, arthritogenic microorganisms, particularly Gram-negative bacteria, could cause and aggravate arthritis; (3) immune activation, including polyclonal B cell activation, Th1 to Th2 switch, increased expression and release of CD38 and class II HLA-DR MHC antigens, etc.[11,22]. HCV infection could synergize with HIV and aggravate the immunological abnormalities in these patients[23-25], as seen in our study.

Clinically, rheumatic manifestations in HIV infection could be classified into 4 categories: (1) mimicry of rheumatic diseases; (2) complication with rheumatic diseases; (3) immunological abnormalities in HIV infection; and (4) importantly, immune reconstitution of inflammatory syndromes caused by HAART therapy[5]. In our study, 7 patients had initiated HAART therapy when studied, and 5 (71.43%) of them had rheumatic manifestations including Behçet-like disease, Sjögren-like syndrome, DILS, polymyositis, and zidovudine-induced myopathy. The inflammatory reaction following institution of HAART is believed to result from an augmented immune response to pathogens that are prevalent in the host but have been clinically occult[5]. It is presumed that these inflammatory syndromes are due to the expansion of pathogen-specific cellular immune reactivity manifesting itself in the presence of strong microbial antigenic stimulation.

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