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Research Article

Seropositivity of HTLV-1 Infection in Inflammatory Arthritis

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Abstract

Background: Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus. It is proposed that in endemic regions of the world, autoimmune disorders related with HTLV-1 contamination such as rheumatoid arthritis are more common. The infiltration of T lymphocyte and hyperplasia of synovial lining cells have also been reported in rheumatoid arthritis and seronegative spondyloarthropathies.

Aim: In this study, we evaluated the etiological relationship between HTLV-1 and inflammatory arthropathies such as rheumatoid arthritis (RA) and seronegative spondyloarthropathy (SPA) in northeastern Iran as this virus is endemic.

Methods: Anti-HTLV-1 antibody was measured in 204 individuals (81 with RA, 43 with SPA and 80 healthy controls). HTLV-1 antibody was evaluated by enzyme-linked immunosorbent assay (ELISA) in serum. For all positive ELISA samples of HTLV-1 infection, Western Blot was performed to confirm the results. Each anti-HTLV-1 and anti-HTLV-2 positive specimens were measured simultaneously to make sure that the test results are true.

Results: The incidence of HTLV-1 contamination in RA group was 6.2%, in SPA group was 2.3% and in control group was 51%. There was not any statistical difference among RA, SPA patients and controls according to the number of HTLV-1 seropositive samples (P **= 005).**

Conclusion: In the present study, we did not find any correlation between HTLV-1 infection and inflammatory arthropathy such as RA and SPA, which suggests that differences in ethnicity may subscribe to this subject. Geographical and environmental factors should be also considered.

Keywords: *Seropositivity; Human T-Cell Lymphotropic Virus Type 1 (HTLV-1); Inflammatory Arthritis; Rheumatoid Arthritis; Seronegative Spondyloarthropathies*

Abbreviations

HTLV: Human T-lymphotropic Virus Type; RA: Rheumatoid Arthritis; SPA: Seronegative spondyloarthropathy; ELISA: Enzyme-Linked Immunosorbent Assay; ATLL: Adult T-Cell Leukemia/Lymphoma; HAM/TSP: HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis; WB: Western Blot; CRP: C-Reactive Protein; RF: Rheumatic Factor

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) belongs to the retrovirus family. This virus is the cause of two human diseases; adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [1,2]. Although the prevalence of the virus in general population is still unknown, according to the estimates, 10 - 20 million people worldwide are infected with HTLV-1 [3-6]. The virus is endemic in southwestern Japan, parts of Africa, Central and South America, and northeastern Iran [7]. The prevalence of HTLV-1 infection in the population of Iran is estimated to be 2.12% [8]. Epidemiological studies suggested that multiple inciting factors including viral infections may be involved in the induction of inflammatory arthropathies [9]. Retroviral infections have been proposed as triggering factor induced autoimmune mechanisms that play a major role in destructive synovitis [10,11]. HTLV-1 may affect the inflammatory arthropathies such as rheumatoid arthritis (RA) with knee, wrist, or shoulder involvements in the absence of clinical ATLL or HAM/TSP; however, no direct evidence has shown that HTLV-1 infection alone induces rheumatic diseases [9,12-14]. Different studies have shown that the HTLV-1 has a critical molecular role in the induction of arthritis. This virus may play a role in some autoimmune disorders including uveitis, alveolitis, polymyositis, Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis (RA) [15-19]. It is proposed that in the endemic regions, autoimmune diseases associated with HTLV-1 contamination are more common [20,21]. For instance, in southern Japan, the prevalence of Sjogren's syndrome and rheumatoid arthritis is five times higher among seropositive HTLV-1 patients than among individuals who are seronegative for HTLV-1 antibody [9,22,23]. HTLV-1 tax protein can develop both inflammatory polyarthropathy resembling RA and non-inflammatory ankylotic arthropathy [24]. This protein lead to the migration of T-lymphocytes into the synovial fluid and synovial tissue, high titers of IgM antibodies against HTLV-1 in the synovial fluid, synovial proliferation, and joint destruction [25,26]. Infiltration of T-lymphocyte and hyperplasia of synovial lining cells play an important role in the pathogenesis of inflammatory arthropathies including RA and seronegative spondyloarthropathies (SPA) [27-29]. In order to investigate the etiological relationship between HTLV-1 and inflammatory arthropathies, we performed a study on patients with RA and SPA in northeastern Iran as an endemic area for this virus.

Materials and Methods

This study was performed on 204 individuals living in Khorasan province in the northeast Iran. The experimental group included 124 patients (81 patients had RA and 43 patients had SPA). Our Control group included 80 people who were recruited from patients' family preferably their siblings matched on gender, ethnic origin, and age with patients group. All patients with RA and SPA diagnosed in Mashhad university hospital and rheumatology clinics based on ACR criteria for RA [30] and criteria for SPA [31]. Mashhad University of Medical Sciences ethics committee approved this study. All participants signed an informed consent. Patients with ATLL, HAM/TSP, and secondary RA and SPA complicating other autoimmune diseases and patients who had risk factors for HTLV-1 infection after RA and SPA involvement (including a history of suspicious sexual contact, intravenous drug users, hospital and laboratory staffs) were excluded from the study. Disease activity in RA was determined by DAS28 based on ESR [32] and in SPA determined by BAS [33]. Demographics and laboratory data, age, sex, duration of RA and SPA, and use of special drugs like disease modifying anti-rheumatic drug (DMARD) were also recorded.

DNA extraction: Five ml blood samples were obtained from each individual and were stored at -20°C. Serum samples were screened for HTLV-1 antibody by enzyme-linked immunosorbent assay (ELISA, Diapro, Italy) according to the manufacturer's instructions. For further confirmation of HTLV-1 infection, all of the ELISA positive samples were confirmed by western blotting analysis (WBI HTLV1 blot 204 kit: gene lab diagnostic, Ltd). Western Blot (WB) with the MP Diagnostics HTLV Blot 2.4 (MP Biomedicals Asia Pacific Pte Ltd, Singapore) was carried out for all positive ELISA samples. Each anti-HTLV-1 and anti-HTLV-2 positive samples (provided by Abbott Diagnostics) were tested simultaneously with the study samples to verify the test results.

Statistical analyses: The statistical analysis was performed using the SPSS16 program (SPSS Inc., Chicago, IL, USA). Values are reported as mean ± standard deviation for normally distributed variables and median with interquartile range (IQR) for others. Kolmogorov-

Smirnov test was applied for normal variable distribution. Two independent proportions test was used to evaluate the statistical difference between frequency of HTLV-1 seropositivity in patients and control groups.

Results

This cross-sectional, case-control study was performed on 204 individuals (81 RA, 43 SPA, and 80 healthy controls). The incidence of HTLV-1 contamination in RA group was 6.2%, in SPA group was 2.3% and in control group was 5.1%. There was no statistical difference in the number of HTLV-1 seropositive samples among RA, SPA and control group (P = 0.05). In 43 SPA patients, only one patient was seropositive for HTLV-1so the statistical analysis of the data was not possible. This patient was an 18-year-old man who was diagnosed with SPA for three years. His presentation was with inflammatory back pain, sacroiliac tenderness, restriction in spinal movements, and arthritis in four peripheral joints. In laboratory data rheumatoid factor (RF) was negative, ESR was 29 mm/h and C reactive protein (CRP) and HTLV-1 were positive.

The mean age of HTLV-1 positive and negative patients in RA group was 56.8 ± 9.04 and 46.72 ± 12.72 years old, respectively. The age of HTLV-1 seropositive patients who have RA was higher than seronegative patients but this difference was not statistically significant. The mean duration of disease in HTLV-1 positive and negative RA patients was 7.61 ± 6.45 and 4 ± 2.58 years, respectively. The incidence of HTLV-1 positivity among women was 9.1% and among men was 5.1%. All 3 patients with RA and HTLV-1 seropositivity were living in northern Khorasan province, including 6.7% of all of patients lived in this area. 61.3% Of RA patients had polyarticular involvement, 31.3% had oligoarticular involvement, and 3.8% had monoarticular involvement. The prevalence of HTLV-1 was 4.1% in polyarticular RA, 12% in oligoarticular RA and zero in monoarticular group. The mean of swollen joints in HTLV-1 positive patients was 4.8 ± 2.28 and in HTLV-1 negative patients were 4.15 ± 2.35. There was no statistical difference between two groups (t = 0.619, df = 4.58, p = 0.565). The incidence of morning stiffness more than 15 minutes was 76.9%. 4 patients (80%) had morning stiffness of more than 15 minutes among 5 HTLV-1 seropositive RA patients. Hand involvement was seen in 87.7% of all of our RA patients and all of our HTLV-1 positive patients were in this group. 22 percent of all patients had extra-articular manifestations and of HTLV-1 seropositive patients, 2 patients (40%) had these manifestations. Rheumatoid nodule was noticed in 8.6% of all patients and nobody was HTLV-1 positive. Joint deformity was noticed in 30.9% of RA patients and of 5 RA patients with HTLV-1seropositivity, only one patient had joint deformity. Eighty percent of our RA patients had positive rheumatoid factor (RF) and 4 patients were RF positive among 5 HTLV-1 positive RA patients. Positive C-reactive protein (CRP) was noticed in 80.3% of all RA patients and in 4 of 5 HTLV-1 seropositive RA patients. In radiographic findings, 60.5% of RA patients had erosion. 3 patients had erosion in hand radiography among 5 HTLV-1 positive RA patients.

	All RA Patients	HTLV-1+	HTLV-1-
Number	81	5 (6.2%)	76 (93.8%)
Mean Age		56.8 ± 9.04	46.72 ± 12.72
Disease Duration		7.61 ± 6.45	4 ± 2.58
Polyarticular (%)	61.3%	40%	63.1%
Oligoarticular (%)	31.3%	60%	29%
Monoarticular (%)	3.8%	0	3.9%
Morning Stiffness > 15 Min (%)	76.9%	80%	76.4%
Swollen Joints (mean)		4.8 ± 2.28	4.15 ± 2.35
Hand Involvement (%)	87.7%	100%	0
Extra-articular Manifestation (%)	22%	40%	21%
Joint Deformity (%)	30.9%	20%	31.5%
RF positivity (%)	80%	80%	64.2%
Positive CRP (%)	80.3%	80%	64%
Erosion (%)	60.5%	60%	60%

Table 1: *Clinical and laboratory features of RA patients.*

Discussion and Conclusion

In the present study, we evaluated the possible role of HTLV-I infection in the development and pathogenesis of RA and SPA in north-eastern Iran, Mashhad. Previous studies have reported the relation between HTLV1 and autoimmune diseases like RA [9,34,35]. However, several investigations failed to detect any relationship between HTLV1 contamination and RA. Among viruses, retroviruses have been considered to be a risk factor [10]. A study in Japan where the retrovirus is endemic has suggested that HTLV-1 plays a role in the pathogenesis of RA [22,26,36]. A study performed in the United States has indicated an association between HTLV-1/2 infection and arthritis [37]. A study conducted in South Africa has failed to demonstrate any association between HTLV-1 infection and RA [38]. The association of HTLV with spondyloarthropathies has not been investigated until now. However, HTLV1 tax gene was responsible for the development of non-inflammatory arthropathies resembling ankylotic arthropathy in transgenic mice [24]. Shortly, pathogenic role of HTLV-I in rheumatoid arthritis and seronegative spondyloarthropaties is still controversial.

On the basis of the data presented here, it appears that the HTLV-I contamination is not associated with seronegative spondyloarthropathy and rheumatoid arthritis. Genetic and environmental factors are important predisposing factors in autoimmune diseases, such as RA or SPA [9,15]. This study revealed that HTLV1contamination is not a predisposing factor for these autoimmune diseases in this endemic area. The association of HTLV1 with inflammatory arthropathy is supported by the detection of high titers of HTLV1 antibody in sera and synovial fluids. As previously mentioned, locally expanded T-cell clones against various antigens and HTLV1 infected synoviocytes are considered to play a role in producing synovial proliferation [38].

Despite the negative association between HTLV1 contamination and RA in our study, we compared the clinical manifestations of seropositive and seronegative patients with RA. we did not find any statistical difference between two groups. However, all 5 patients with positive HTLV1 and RA had more than 3 tender and swollen joints, hand joints involvement and symmetric arthritis. Four of 5 HTLV1 positive patients had morning stiffness greater than 15 minutes, positive CRP and positive RF. As the prevalence of seropositivity increases with age in both men and women in general, it seems natural that the age of seropositive patients with RA was higher than that of seronegative patients, although it was not significant.

The strength point of this case-control study was carrying out of the study in an endemic area. Taken together, our results showed that there is no correlation between HTLV-I contamination and development of RA and SPA which suggests that differences in ethnic background may contribute to this issue. Geographical and environmental factors should be considered. Because of the relatively small number of our patients, our results do not negate the possibility of exogenous or endogenous retroviruses role in the etiology of autoimmune diseases such as RA or SPA.

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