Original Article

Prevalence of Human T-lymphotropic virus type 1 (HTLV-1) Infection in Patients with Hematologic Disorders and Non-Hematologic Malignancies in a Tertiary Referral Hospital

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Abstract

Background: Human T-lymphotropic virus type 1 (HTLV-1) was the first retrovirus identified in human. The current evidence is quite scarce regarding the potential role of HTLV-1 in pathogenesis of hematologic disorders and non-hematologic malignancies.

Objectives: The aim of this study is to evaluate the prevalence of HTLV-1 infection in patients with hematologic disorders and non-hematologic malignancies.

Methods: This cross-sectional study was conducted on 505 cases of definite diagnosis of hematologic disorders including malignancies as well as non-malignant disorders such as polycythemia and myelofibrosis and non-hematologic malignancies referred to the hematology and medical oncology ward at Army Hospital 501 from January 2015 to January 2016. A 3-mL blood specimen was collected from each patient and tested for the presence of anti-HTLV-1 antibodies using enzyme-linked immunosorbent assay (ELISA). Data were analyzed using SPSS software package version 19 (IBM, New York, USA). Data are presented as mean ± SD if normally distributed and otherwise as median (range).

Results: Totally, 242 (48%) males and 263 (52%) females with a mean ± SD age of 52.09 ± 16.24 were enrolled in this study. In total, there were 9 (1.78%) cases positive for HTLV-1 infection including 4 males and 5 females. Seven out of 287 (2.4%) patients with hematologic disorders were infected by HTLV-1. In non-hematologic malignancies, 2 out of 211 cases were positive (0.9%). There was no HTLV-1 positive case in 7 patients with both hematologic and non-hematologic disorders. The difference in HTLV-1 infection prevalence between patients with hematologic disorders and non-hematologic malignancies was not statistically significant different (P = 0.31). There was no association between sex and transfusion history with HTLV-1 infection in this population (P = 0.9 and 0.7, respectively).

Conclusions: Our study revealed that the prevalence of HTLV-1 in hematologic disorders is higher than the general population. Further larger prospective studies are recommended to corroborate the current evidence.

Keywords: HTLV-1, malignancy, prevalence

Cite this article as: Jalaeikhoo H, Soleymani M, Rajaeinejad M, Keyhani M. Prevalence of Human T-lymphotropic virus type 1 (HTLV-1) Infection in Patients with Hematologic Disorders and Non-Hematologic Malignancies in a Tertiary Referral Hospital. *Arch Iran Med*. 2017; 20(4): 224 – 228.

Introduction

Human T-lymphotropic virus type 1 (HTLV-1), the first retrovirus identified in human, was discovered in 1979.[1,2]

The diagnosis of HTLV-1 infection was first reported in a patient with cutaneous T-cell lymphoma.[2] This retrovirus can be transmitted through breast feeding, sexual intercourse and blood contact.[3] Epidemiological evidence has demonstrated an association between HTLV-1 infection and adult T-cell leukemia/lymphoma (ATL), HTLV-1 associated myelopathy / tropical spastic paraparesis (HAM/TSP) and HTLV-associated uveitis (HAU).[3] Due to the immunosuppressive effect of HTLV-1, it can cause opportunistic co-infections such as tuberculosis and strongyloidiasis,[4] although this infection remains asymptomatic in many carriers throughout their life.[5]

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Accepted for publication: 28 February 2017

The global prevalence of HTLV-1 is about 15–20 million people, although there is not enough evidence to provide the exact number of seropositive individuals worldwide.[6] Some endemic areas are southwestern Japan, the Caribbean basin, several sub-Sahara African countries and localized areas in Iran and Melanesia.[3,7] In Iran, Mashhad was introduced as an endemic region of HTLV-1 in 1996.[8,9] Based on geographic and specific groups of individuals (e.g., blood donors, patients with thalassemia major, etc.), the prevalence rates of HTLV-1 infection differ in studies carried out in Iran.[8–16]

Although some studies have shown the association of HTLV-1 infection with hematologic malignancies like ATL and lymphosarcoma T-cell leukemia,[17,18] current evidence is quite scarce on the prevalence of HTLV-1 infection in other malignancies such as stomach cancer, colon cancer, breast cancer, and lung cancer in Iran.

Objectives

The aim of this study is to determine the prevalence of HTLV-1 infection in patients with hematologic disorders and non-hematologic malignancies.

Patients and Methods

This cross-sectional study was conducted in the hematology and medical oncology ward at Army Hospital 501 from January 2015 to January 2016. All patients with definite diagnosis of hematologic disorders including malignancies such as AML, ALL, CML, CLL, lymphoma, plasmacytoma and myelodysplastic syndromes as well as non-malignant disorders including iron deficiency anemia, idiopathic thrombocytopenic purpura, thalassemia, polycythemia and myelofibrosis were included in this study. Moreover, patients with non-hematologic malignancies such as cancers of colon, breast, ovary, stomach, lung, etc. were also invited to participate in the study. Patients received verbal and written information and gave informed consent. The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. A 3-mL serum specimen was collected from each patient and was stored at room temperature before testing. The participants were screened for the presence of HTLV-1 specific antibodies using an enzyme-linked immunosorbent assay (ELISA, Diapro kit). Laboratory testing for HTLV-1 infection is routinely performed in Iranian Blood Transfusion Organization (IBTO). This study was approved by the ethics committee of AJA University of Medical Sciences.

Statistical Analysis

Data were analyzed using SPSS software package version 19 (IBM, New York, USA). Data are presented as mean ± SD if normally distributed and otherwise as median (range). Chi-square test or Fisher's exact test were performed to compare the prevalence of HTLV-1 infection between patients with hematologic disorders and those with non-hematologic malignancies.

Results

Characteristics of the study population

A total of 505 patients were enrolled in the study. Of these, 242 (48%) were males and 263 (52%) were females. The average ± SD age of the study population was 52.09 ± 16.24 (ranging from 13 to 87) years (Table 1).

Serologic results

In total, 9 out of 505 samples (1.78%) including 4 males and 5 females were positive for anti-HTLV1 antibody using the ELISA assays. Of the HTLV-1 positive cases, two were diagnosed with T-cell acute lymphoblastic leukemia. Furthermore, T-cell lymphoma, B-cell non-Hodgkin lymphoma (NHL), T-cell NHL, acute myeloblastic leukemia, anemia/spastic paralysis, lung cancer and colon cancer, were each diagnosed in one case (Table 2). The prevalence of HTLV-1 infection in patients with hematologic disorders was 2.4%. Among HTLV-1 positive patients, three cases originated from Mashhad; West Azerbaijan and Tehran had two cases each, and one case originated from Hamedan. Four patients (44.4%) had positive transfusion history.

We also investigated the prevalence of HTLV-1 infection in patients diagnosed with non-hematologic malignancies. The prevalence of HTLV-1 in patients with non-hematologic malignancies was 0.9% in our study (two out of 211 patients). Positive patients were diagnosed with lung cancer and colon cancer. The difference of HTLV-1 infection prevalence between patients with hematologic disorders and non-hematologic malignancies was not statistically significantly different ($P = 0.31$). There was no association between sex or transfusion history with HTLV-1 infection in this population ($P = 0.9$ and 0.7, respectively). The two positive patients were 75 and 63 years old.

Table 1. Comparison of demographic features of patients with hematologic disorders and non-hematologic malignancies.

	Hematological disorders ($n = 287$)	Non-hematologic malignancies ($n = 211$)	Both ($n = 7$)
Age (mean± SD)	48 ± 17	57 ± 12	48.2 ± 16.2
Sex (M/F)	163/124	77/134	2/5
Transfusion history	136 (47.4%)	88 (41.7%)	4 (57.1%)
HTLV-1 positive	7 (2.4%)	2 (0.9%)	

Table 2. Characteristics of HTLV-1 positive patients.

	Sex	Age	City	Diagnosis	Transfusion history
1	Male	43	Mashhad	T-ALL	Pos
2	Female	23	Tehran	AML	Neg
3	Female	45	Hamedan	T-ALL	Neg
4	Female	30	Shahriyar	T-cell NHL	Pos
5	Female	61	Mashhad	Anemia/spastic paralysis	Neg
6	Male	43	Orumiye	B-cell NHL	Pos
7	Male	52	Maku	T-cell Lymphoma	Neg
8	Male	75	Tehran	Lung cancer	Pos
9	Female	62	Mashhad	Colon cancer	Neg

Pos = positive, Neg = negative

Discussion

HTLV-1 infection is a risk factor for hematologic disorders, especially malignancies like ATL and lymphosarcoma T-cell leukemia[17,18] through the oncogenic effect of TAX and HBZ viral proteins. These proteins cause hyperproliferation and suppress cell cycle progression in infected cells including CD4+ and CD8+ T-lymphocytes.[19–22]

Obligatory transfusion in some hematologic disorders like thalassemia may result in HTLV-1 transmission.[23] Furthermore, epidemiologic studies have shown a relationship between some immunologic disorders and HTLV-1 infection. Rheumatologic disorders and autoimmune mediated diseases including Graves, Rheumatoid arthritis, Sjögren's syndrome, and HAM/TSP, are among immunologic disorders which are previously shown to be associated with HTLV-1 infection. Also, the infected individuals are more susceptible to opportunistic co-infections.[24–27]

Immunosuppressive effects of HTLV-1 support the hypothesis of potential etiologic role of HTLV-1 infection in non-hematologic cancers like colon cancer, breast cancer, lung cancer, etc. However, some evidence show a protective effect of HTLV-1 infection on gastric carcinoma thorough suppressing inflammation in *Helicobacter pylori* infection.[28,29] In addition, recent studies demonstrate the relation of thymoma and positive result for TAX gene.[30]

According to these mechanisms, a higher prevalence of HTLV-1 infection in hematologic patients compared to the general population was supposed. In this study, we demonstrated that this concept is approximately true. The prevalence of HTLV-1 in the general population in Mashhad, the most prevalent area of Iran,[9] Golestan province[15] and Sabzevar[11] was 2.12%, 0.3% and 1.66% respectively, which is on the average lower than what we observed in patients with hematologic disorders in our study.

In the present study, we demonstrated that the prevalence of HTLV-1 infection among patients with hematologic disorders is 2.4% (7 out of 287 patients). Except one positive patient whose diagnosis was anemia/spastic paralysis, the other patients were diagnosed with hematologic malignancies including leukemia and lymphoma. Several studies have suggested that the prevalence of HTLV-1 rises with age[31–35]; in this study, the mean age of positive patients was lower compared to the overall population. The prevalence of HTLV-1 infection was slightly higher in females (1.9%) compared to males (1.6%). Moreover, there was no remarkable association between transfusion history and HTLV-1 infection.

There are several previously published articles which have reported the prevalence of HTLV-1 infection from different geographic regions of Iran. The prevalence of HTLV-1 infection in 101 patients with hematologic disorders, including lymphoma, leukemia, thalassemia and hemophilia, in Isfahan was 0.99% from April to October 2012.[36] Monavari *et al*. found a prevalence of 20% in 60 patients with hematologic malignancies (leukemia and lymphoma) in Tehran.[37] The prevalence of HTLV-1 in 54 patients with non-Hodgkin lymphoma in Mashhad was reported to be 18.8%.[38] It appears that the diversity in diagnostic methods and study population beside small sample size are the most important causes of this variation in results; for instance, the results of the last two studies are significantly different from ours which may be due to their too small sample size. Furthermore, about 70% of the sample size of both studies were males and it was previously demonstrated that the prevalence is higher in males.[39,40] Moreover, the sample population of these two studies consisted of individuals diagnosed with hematologic malignancies and other hematologic disorders were not considered in these two studies. Their diagnostic method was PCR which is more accurate for diagnosing HTLV-1 infection compared to ELISA.

Studies from other countries also show variable results. In a study conducted in Rio de Janeiro, Brazil, the prevalence of HTLV-1 infection in 510 hematologic patients without previous blood transfusion was 9.01% in which the most prevalent subgroup was T-cell disease with the prevalence of 28.9%.[41] In Lagos, Nigeria, the seroprevalence of HTLV-1 infection among 39 cases of lymphoid malignancies was 5.12%.[42] The reported seroprevalence of HTLV-1 in 88 patients with hematologic malignancies in south Chile was 3.4%. Interestingly, in this study the prevalence obtained through PCR was 18.2%.[43] A prevalence of 23% was found among 100 patients with malignant nodal lymphoma in Okinawa, Japan.[44]

S.N.E Tahaei *et al.* conducted a case-control study on 201 gastric and colorectal cancer patients and reported the prevalence of 0.49% in cancerous patients and 1.8% in controls which confirms the protective effect of HTLV-1 infection on gastric cancer.[45] Studies in Iran have demonstrated that HTLV-1 infection has no relation with cervicovaginal cancer and Kaposi's sarcoma.[46,47] The prevalence of HTLV-1 infection in 279 cancer patients in Kerala state, India was 3.2%.[48] In a cohort study on 4136 subjects with 6-year follow-up, the authors concluded that HTLV-1 is not associated with an increased risk of cancers of colon-rectum, biliary tract and lung. However, it increases the risk of liver cancer (RR = 1.4) and cervical cancer (RR = 8.3). In addition, the significantly protective effect of HTLV-1 infection on gastric cancer was demonstrated in this study (RR = 0.42, 95% CI = 0.17–0.99).[28]

Our study has several limitations which should be carefully considered when interpreting our findings. First, this study was conducted in a tertiary referral center with small sample size which limits the generalizability of our findings. Furthermore, our diagnostic method was ELISA while the gold standard method for HTLV-1 is PCR. This could affect the accuracy of our results.

In conclusion, our results show a higher prevalence of HTLV-1 infection in patients with hematologic disorders in comparison to other studies conducted on the Iranian general population.[49] However, we could not make a definite conclusion about the association of HTLV-1 infection and hematologic disorders due to lack of control group. Larger prospective studies with more accurate diagnostic methods of HTLV-1 are essential to corroborate the evidence.

Ethical approval

This study was approved by the ethics committee of AJA University of Medical Sciences.

Financial disclosure

The authors have no financial disclosure to declare.

Acknowledgments

Special thanks are given to the staff of the hematology and medical oncology ward at Army Hospital 501, AJA University of Medical Sciences.

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