



HTLV1 Infection in Patients with Common Endogenous Dermatitis

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Abstract

Background: Human T-cell Lymphotropic Virus type I (HTLV1) infection has been reported in patients with a variety of skin lesions in some parts of the world, especially in endemic areas. Infective Dermatitis associated with HTLV-1 (IDH) is the prototypic dermatologic manifestation of infection. However, to the best of our knowledge, it has not been reported in Iran as an endemic area yet. It is aimed to investigate the prevalence of HTLV1 infection among patients with common endogenous dermatitis.

Methods: During a cross-sectional study, blood samples of 100 patients with both clinical and pathological diagnoses of common endogenous dermatitis including atopic, seborrheic, and nummular dermatitis who were referred to the Dermatology Clinic of Ghaem and Imam Reza Hospitals, Mashhad, Iran were obtained and evaluated for the presence of anti-HTLV-1 antibody using the ELISA method. The Polymerase Chain Reaction (PCR) for HTLV-1 was conducted in cases where the anti-HTLV1 antibody was positive. Statistical analysis was performed using SPSS version 16, Chicago, IL, USA.

Results: Among 100 samples, two cases including erythrodermic dermatitis and atopic dermatitis were positive according to the ELISA method (2.0%). The dermatitis in HTLV1-positive patients was erythematous, scaly, with a generalized distribution and a recurrent nature, but did not complete the Infective Dermatitis (ID) criterion.

Conclusion: In Iran as an endemic area, HTLV1-associated dermatitis may be present as recurrent generalized erythematous and scaly rash instead of known typical features of infective dermatitis.

Keywords: Atopic dermatitis, Enzyme-linked immunosorbent assay, Human T-lymphotropic virus 1, Polymerase chain reaction

Introduction

Human T Lymphotropic Virus type 1 (HTLV1) infection in humans is responsible for Adult T cell Leukemia/Lymphoma (ATLL) and HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) (1) as well as certain dermatological manifestations including Infective Dermatitis associated with HTLV1 (IDH), xerosis, acquired ichthyosis, seborrheic dermatitis and parasitic dermatosis. Other skin comorbidities associated with IDH such as dermatophytosis, scabies, particularly Norwegian scabies, and bacterial infections can also be observed in HTLV1 patients due to impaired immunity (2,3).

There is an estimation of about 10 to 20 million infected around the world. Various sub-types of HTLV-1 were reported from southwest Japan, Taiwan, the Caribbean basin, Central and South America and Africa, Romania, south Italy, the North Pole, and northern Iran with an average age at diagnosis of 50 to 70 years (4-6).

HTLV-1 carriers are estimated to be 10 to 20 million worldwide. However, HTLV-1 infection is only associated with a 3-5% risk of ATL development (7). IDH is defined as chronic and recurrent eczema occurring mostly in childhood and infrequently in adolescence or adulthood (8,9). It often begins with a rhinitis identified by the child's mother as a "cold" and followed by an oozing, eruption and weeping on many body areas. The lesions are erythematous, scaly, and frequently covered by yellow and fetid crusts (10). The most important differential diagnosis of IDH is Atopic Dermatitis (AD). Both diseases are susceptible to infection of the lesions by *Staphylococcus aureus* (*S. aureus*); however, infection is more marked in IDH. A childhood onset is also shared by both conditions. Positive family history is a feature that characterizes AD (11).

Despite the high prevalence of HTLV-1 in north-eastern Iran, IDH has not been recognized in Iran, yet. Thus, in the current study it is aimed to investigate the prevalence of HTLV-1 infection in patients with common endogenous dermatitis including AD as well as seborrheic and nummular dermatitis.

Materials and Methods

The study was conducted as a descriptive

cross-sectional study during 2012-14 in Imam Reza and Ghaem University Hospitals, Mashhad, Iran. Following approval from the ethics committee of Mashhad University of Medical Sciences and obtaining written informed consent, 100 patients with common endogenous dermatitis including AD, seborrheic dermatitis, nummular and erythrodermic dermatitis were enrolled in the study.

As the first step, demographic variables as well as clinical history and dermatological examination including the type of dermatitis, extent of involvement and number of recurrent episodes were obtained and recorded in a pre-designed form. Patients were divided in to 5 groups according to the extent of skin involvement: <10%, 10-25%, 25-50%, 50-75% and 75-100% Body Surface Area (BSA). For the second step, 6 ml blood samples were taken from the brachial vein for the HTLV-1 laboratory test. Three ml were used for serum preparation and 3 ml of EDTA was used for Peripheral Blood Mononuclear Cells (PBMCs) separation. Serum samples were evaluated for HTLV-1 antibody using an Enzyme-Linked Immunosorbent Assay (ELISA) kit according to manufactures' instruction (ADALTIS kit, Italy). In order to confirm HTLV I, Polymerase Chain Reaction (PCR) was performed on all positive ELISA samples. PBMCs were collected from positive samples by the Ficol method following DNA extraction. PCR was carried out using specific primers for tax and LTR regions as previously described (12).

Statistical analysis

Descriptive and inferential statistics were used to analyze the data by the Statistical Package for the Social Sciences software (SPSS version 16, Chicago, IL, USA). Central dispersion indices, mean and standard deviation were used to describe the data.

Results

Skin dermatoses

Among 100 patients, 39 cases (39%) were male and 61 cases (61%) were female. The mean age of the patients was 42.58 ± 23.80 years (from 1 year to 87 years old). Demographic characteristics and clinical data findings of the patients are presented in table 1. Erythrodermic dermatitis (38.5%) and AD (38.5%) were more common in men, while atopic dermatitis

Table 1. Demographic characteristics of patients based on dermatitis type

Dermatitis type	Number	Male N (%)	Female N (%)	Mean age (years)
Seborrheic dermatitis	19	7(17.5%)	12(19.7%)	39.05±18.13
Erythrodermic dermatitis	31	15(38.5%)	16(26.2%)	54.26±23.03
Atopic dermatitis	47	15(38.5%)	32(52.5%)	35.66±23.76
Nummular dermatitis	3	2(5.1%)	1(1.6%)	52.67±25.11
Total	100	39(100%)	61(100%)	42.58±23.80

(52.5%) was more common among women. According to table 1, the lowest and highest patients' ages were observed in AD (35.66±23.76 years old) and erythrodermic dermatitis (54.26±23.03 years old), respectively. The skin involvement among patients were as follows: 75-100% skin involvement: 37% of patients, 50-75%: 7%, 25-50%: 16%, 10-25%: 17%, and 10> %: 23% of patients (Table 2).

The most skin involvements according to each dermatosis are as follow: among seborrheic dermatitis patients, 11 patients (57.9%) had <10% skin involvement; 14 patients with AD had 10-25% skin involvement (29.8%) and <10% of skin involvement was seen in 2 patients with nummular dermatitis (66.7%). Forty-six patients had no history of relapsing lesions (46%), while 35 patients (35%) had more than 3 relapsing episodes (Table 2).

HTLV-1 assay

Among 100 cases, 2 patients (2%) were found to

have positive HTLV-1 by ELISA, subsequently confirmed by PCR. According to PCR, two patients were HTLV-1 positive: a 73-years-old man with erythrodermic dermatitis and a 56-years-old woman with AD. The extent of skin involvement in both positive HTLV1 cases was 75-100%.

The first case was a 73 years old man with erythrodermic dermatitis and generalized involvement with the second occurrence of skin symptoms. The skin biopsy showed an orthokeratotic epidermis, hydropic degeneration of the basal layer cells, moderate spongiosis and inflammatory cell exocytosis. The patient had no other organ involvement due to HTLV-1. The second case was a 56-years-old woman with AD and generalized involvement and her third episode of skin lesions relapsing. The patient's symptoms included erythematous, scaly lesions specifically on the scalp, upper limbs and trunk. There was also a history of neglected myalgia and arthralgia during 6 months before admission. The

Table 2. Extent of involvement and frequency of relapsing based on type of dermatitis

Dermatitis type		Extent of involvement (%)					Relapsing				Total
		>10	10-25	25-50	50-75	75-100	0	1	2	≥3	
Seborrheic dermatitis	Number (%)	11(57.9)	2(10.5)	5(26.3)	0	1(5.3)	2(10.5)	2(10.5)	2(10.5)	13(68.4)	19(100)
Erythrodermic dermatitis	Number (%)	0	1(3.2)	3(9.7)	0	27(87.1)	24(77.4)	2(6.5)	1(3.2)	4(12.9)	31(100)
Atopic dermatitis	Number (%)	10(21.3)	14(29.8)	8(17)	7(14.9)	8(17)	19(40.4)	5(10.6)	6(12.8)	17(36.2)	47(100)
Nummular dermatitis	Number (%)	2(66.7)	0	0	0	1(33.3)	1(33.3)	1(33.3)	0	1(33.3)	3(100)
Total	Number (%)	23(23)	17(17)	16(16)	7(7)	37(37)	46(46)	10(10)	9(9)	35(35)	100(100)

patient was subsequently diagnosed with ATLL after further work up and was referred to a haematologist.

Discussion

Skin manifestations of HTLV-1 infection range from xerosis to IDH, the prototypic sign which occurs during childhood (6,9). A peculiar feature of IDH is that it occurs in certain ethnics such as Caribbeans, Jamaicans and sub-Saharan Africa. Iran and Japan are known as endemic areas, however, IDH has not been reported yet in these countries (3). Gessain *et al* have reported that among the 2,500 children examined at a dermatological center in Dakar, Senegal over a three year period 5 were diagnosed with typical ID related to HTLV-1 infection (1). The diagnosis of IDH is principally clinical and the main differential diagnosis of IDH are atopic and seborrheic dermatitis (13). Positive serology for HTLV-1, although helpful, is not enough for a definite diagnosis, which is based on proposed major and minor criteria (14,15). Batista *et al* showed that the high Proviral Load (PVL) in IDH patients does not necessarily indicate progression to HAM/TSP. PVL did not decrease after IDH improvement. Maintaining a high PVL after recovery can favor early ATL development. Therefore, IDH patients should be followed up for a long time even after IDH recovery (9). In 1998, La Grenade *et al* proposed a diagnostic criterion for IDH, the most important of which are: 1) Eczema on the scalp, as well as armpits, groin, retroauricular region, ear canal, eyelids, paranasal regions, and neck (at least three sites are necessary, including the scalp and retroauricular region); 2) Chronic rhinorrhea; 3) Recurring chronic dermatitis which immediately responses to oral antibiotics; 4) Early onset in childhood; 5) Positive serology for HTLV-1. The diagnosis is confirmed under four criteria, with criteria 1, 3, and 5 being mandatory (15).

With respect to the high prevalence of HTLV-1 in North-Eastern Iran and no reports of IDH, some theories should be taken into consideration. One probable reason maybe the lack of sufficient attention to the symptoms and defined diagnostic criteria of IDH leading to false diagnosis of infectious atopic or seborrheic dermatitis. Hence, in this study it was aimed to investigate the prevalence of HTLV-1 infection in patients with common endogenous

dermatitis including atopic, seborrheic and nummular dermatitis.

The results revealed two positive HTLV-1 cases (2%), including a 73-years-old man with a second recurrence of erythrodermic dermatitis and a 56 years old woman with a third recurrence of generalized AD. Yazdanpanah *et al* performed an investigation to compare the dermatological outcomes of HTLV-1 carriers among 100 blood donors who were identified by the Blood Transfusion Organization and healthy people as the control group in Mashhad, North-Eastern Iran. The frequency of aphthous stomatitis, eczema, and non-genital warts in the case group was significantly higher than the control group ($p < 0.05$) (16).

La Grenade *et al* reported 14 Jamaican children with infective dermatitis who were HTLV-1 positive. Among these patients, 2 cases developed ATLL and HAM/TSP within 17 to 25 years later. It was also concluded that HTLV-1 infection is associated with other dermatitis such as AD (17). Shohat *et al* reported HTLV-1 infection in a 32-years-old woman presented with chronic AD and distal lower limb parasthesia (18). Although there is some evidence confirming the relation between HTLV-1 infection and AD, the exact cause-effect relationship or co-occurrence between AD and HTLV-1 infection is still unclear. Likewise, in the current study, we can not confirm such a relation or specific clinical pattern in HTLV-1 patients since few numbers of HTLV-1 patients were detected and both of them had generalized involvement as well as frequent recurrence of dermatitis. These are in accordance with previous findings by Yazdanpanah *et al* (16). No previous report of typical IDH in Iran, as an HTLV-1 endemic region, versus high prevalence in Caribbean's countries imply the possible role of some other factors in development of HTLV-1 related skin manifestations including environmental and genetic backgrounds, which result in various immune-genetic responses to infection and lead to different clinical presentations (19). Also, familial clustering of IDH and HAM/TSP in some HTLV-1 patients and their strong associations suggest possible genetic backgrounds (20). In Japan as one of the endemic areas IDH has rarely been reported. Japanese patients with HAM/TSP show a different immune-genetic

background to HTLV-1 (21).

The previous report of Shohat reported that HLA-A antigen found in HTLV-1 patients presented with AD was very similar to those found in ATLL and HAM/TSP (18). Moreover, recent studies have shown that the basic leucine zipper factor (*HBZ*) gene is transcribed in all adult HTLV-1 infected patients, including ATLL, HAM/TSP and asymptomatic carriers, whereas tax mRNA was only transcribed in half of these groups. Batista *et al* in a study on 31 adolescences with IDH stated that the *HBZ* gene plays a role in the development of IDH (22).

Given that, unlike the low prevalence of IDH as a prototypic skin manifestation of HTLV-1 infection in Iran, other complications of HTLV-1 infection such as ATLL and HAM/TSP have been widely reported. It could be due to various factors including the difference in phylogeny of the virus in this region, from Jamaica and Caribbean, Human Leukocyte Antigen (HLA) differences, and environmental factors (23).

Limitations

The findings of this study should be considered in light of some limitations. The major limitation of this study is the lack of a control group. On the other hand, the study was conducted based on the samples of two major university hospitals in Mashhad, Northeast Iran, where most of the referral patients from other areas of the state are admitted.

Considering the overall HTLV-1 prevalence was

estimated at 2.12% among the general population of Mashhad (24), having a control group could result in a higher level of reliability of the study.

Thus, one should be careful to expand the results of this study to another area. Moreover, small sample size and high heterogeneity of samples may have affected the accuracy of the results.

Conclusion

Although in several endemic areas for HTLV-1, such as Jamaica and Brazil, IDH has been reported as the main skin manifestation of HTLV-1, other manifestations, including recurrent endogenous dermatitis, may be seen in another endemic area. Clinicians should consider HTLV-1 serology when dermatitis relapses after the appropriate therapy or when there is a family history of HTLV-1 in the endemic areas.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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