Dermatologic Manifestations in HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis

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Abstract- The human T cell lymphotropic virus type-1 (HTLV-1) is associated with adult T cell leukemia/lymphoma (ATL) and other disorders, including a slowly progressive demyelinating paraparesis, known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Dermatologic manifestations are common in patients infected with HTLV-1 infection. In this study, we evaluated the dermatologic lesions associated with HAM/TSP patients in Mashhad, Iran. Dermatological findings of 37 patients with HAM/TSP were investigated and compared with those of an HTLV-1 negative control group. A cutaneous biopsy was performed as needed, and the results were statistically analyzed. Results of the present study showed that 34 cases with HAM/TSP (91.9%) and 24 cases in the control group (64.9%) had at least one skin lesion or history of skin lesion before (P=0.010). Xerosis was found in 22 persons (59.5%) in the case group and 4 persons in the control group (10.8%) (P=0.000). Only xerosis was significantly associated with HAM/TSP. Skin manifestations were quite frequent in patients with HAM/TSP. Xerosis was significantly associated with HAM/TSP.

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Introduction

The human T cell lymphotropic virus type-1 (HTLV1) is a virus from the retrovirus family which is associated with the development of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia/lymphoma [ATLL] (1,2). Cutaneous manifestations are common among HTLV1 infected patients. Patients with HAM/TSP may have skin manifestations such as infectious dermatitis, (3) xerosis , palmar erythema, cutaneous candidiasis (4) and scabies (5). Approximately 50% of patients with adult T cell leukemia/lymphoma have some kind of skin manifestations. This is an important factor to diagnose and predict the prognosis of ATLL (6). In contrast with ATLL, there are only a few studies dealing with the cutaneous manifestation of HAM/TSP. In the present study, we aimed to evaluate the skin manifestations associated with HAM/TSP. The study was done in the city of Mashhad in the northeast of Iran which is an endemic area for the HTLV1 infection (7). For the patients suspicious to HAM/TSP, demonstration of the skin manifestations could be helpful in the disease diagnosis in its early stage. Also, these skin manifestations could be a good indication in the endemic area to evaluate the HTLV1 infection. This could result in the early diagnosis and prevent the disease spread in the community.

Materials and Methods

This was a case-control study. The case group

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consisted of patients with HAM/TSP which had been referred to the neurology clinic of Quaem hospital during 2005-2006. Their disease was confirmed by CSF evaluation for anti-HTLV1 antibody or by PCR in some cases. The control group was selected from those blood donors whose HTLV1 infection was negative in their Elisa tests. Their sex and age were also matched with those of the case group. Both groups were examined by a dermatologist for any skin manifestations. Additionally, skin biopsy was performed to confirm the diagnosis in some cases.

Myelopathy severity was accessed by neurologists and was ranked from 1-13 according to motor disability score of HTLV1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) (8). The scores are described in table 1.

The obtained results were classified as mild myelopathy (scores from 1-4), moderate myelopathy (scores from 5-8), and severe myelopathy (score from 9-13).

Table 1. Osame's Motor disability score

	Motor Disability score
1	Normal gait but run slowly
2	Abnormal gait (staggering or spastic)
3	Abnormal gat an unable to run
4	Needs support while using stairs but walks without assistance
5	Needs one hand support in walking
6	Needs two hands to support in walking (can walk mort ha 10m)
7	Needs two hands to support in walking (can walk less than 10 m)
8	Needs two hands to support in walking (can walk less than 5 m)
9	Unable to walk but can crawl on all fours
10	Unable to crawl on all fours but can crawl with the hands
11	Unable to crawl on hands but can turn sideways in bed
12	Unable to can turn sideways in bed but can move the toes
13	Completely bedridden (unable to move the toes)

Results

Overall, 37 patients with HAM/TSP were enrolled in the case group, and 37 persons with negative HTLV1 test were enrolled in the control group. Both groups were accessed for skin lesions.

There were 28 females (75.7 %) and 9 males (24.3%) in the case group while 26 females (70.3%) and 11 males (29.7%) in the controls (P=0.601). The mean age of patients was 42±14.2 years (max=70 and min=15) in the case group and 41.2±14.2 years (max=75 and min=18) in the control group (P=0.224).

The severity ranking of myelopathy based on the motor disability score showed that 28 patients (82.4%) had mild myelopathy and 6 (17.6%) patients had moderate myelopathy. There were no patients with severe myelopathy in our study. Twenty-nine patients (78.4%) were suffering from myelopathy for less than 10 years and 8 patients for more than 10 years.

Results showed that 34 persons (91.9%) in the case group and 24 (64.9%) in the control group had at least one skin lesion or had a history of skin lesion before (P=0.010). Twenty-five patients (89.3%) with mild myelopathy had skin lesions while all the patients with moderate myelopathy had skin lesions. Skin manifestation was significantly higher in patients with moderate myelopathy compared with the patients with mild myelopathy (P=0.005, using correlation test). So, our results showed that skin manifestations had a direct correlation with severity of myelopathy.

Table 2 summarizes the main dermatological findings in the present study. As shown in the table, xerosis was the most common manifestation in the case group. Also, it was significantly more common in the case group compared with the control group (P=0.000). The mean age of the patients with xerosis was 45 years old in the case group and 37.7-year-old in the control group (P=0.374).

From 22 patients with xerosis in the case group, 18 patients (82%) were female, and 4 (18%) were male. Fifteen (53.6%) out of 28 patients with mild myelopathy and 5 (83.3%) out of 6 patients with moderate myelopathy had xerosis (P=0.004).

Evaluation of the relationship between frequencey ofxerosis and the duration of myelopathy showed that xerosis is significantly more frequent in the second decade of myelopathy than it was in the first decade (P=0.011), table 3.

Table 2. Dermatologic findings in patients with HTLV1 associated HAM/TSP and HTLV1 negative control subjects

Dermatological finding	No (%) of patients with HAM/TSP	No (%) of control subjects	*P*
Skin abnormality	34(92%)	24(65%)	0.010
Xerosis	22(59.5%)	4(10.8%)	0.000
Herpes zoster scar	5(13.5%)	0	0.054
Itching	5(13.5%)	1(2.7%)	0.199
Leishmaniasis	0	3(8.1%)	0.24
Herpes labialis	15(40.5%)	10(27%)	0.326
Seborrheic keratosis	4(10.8%)	1(2.7%)	0.354
Tinea versicolor	2(5.4%)	0	0.493
Keratosis pilaris	2(5.4%)	0	0.493
Drug reaction	0	2(5.4%)	0.493
Psoriasis	3(8.1%)	1(2.7%)	0.615
Wart	4(10.8%)	2(5.4%)	0.674
Aphthous stomatitis	6(16.2%)	8(21.6%)	0.768
Eczema	7(18.9%)	7(18.9%)	1.000
Nonspecific chronic dermatitis	3(8.1%)	5(13.5%)	0.711
Seborrheic dermatitis	4(10.8%)	2(5.4%)	0.674
Acne vulgaris	2(5.4%)	2(5.4%)	1.000
Cherry red angioma	2(5.4%)	2(5.45)	1.000
Palmar and plantar erythema	1(2.7%)	0	1.000
Urticaria	1(2.7%)	0	1.000
Oral pigmented macule	1(2.7%)	0	1.000
Depigmentosus nevus	1(2.7%)	0	1.000
Vascular nevus	1(2.7%)	0	1.000
Skin tag	1(2.7%)	2(5.4%)	1.000
Fungal infection	1(2.7%)	2(5.4%)	1.000
Lichen planus	0	1(2.7%)	1.000

Table 3. The frequency of xerosis based on the duration of HAM/TSP

Duration HAM/TSP	No(%) of patients with xerosis	no(%) of patients without xerosis	*P*
1-10 years	16(55.2%)	13(44.8%)	*P*=0.011
11-20years	6(75%)	2(25%)	

Discussion

Although infective dermatitis is the only skin disorder which has been established to be associated with HTLV1 infection, (9,10) other skin disorders are also common among HTLV1 infected and HAM/TSP patients. In the present study, the dermatological findings for the patients with HTLV1 associated HAM/TSP were evaluated and compared with those of the seronegative control group. It showed that the skin involvement in the patients with HAM/TSP was more frequent than those in the control group (91.9% skin manifestation in the patients with HAM/TSP while 64.9% in the control group). These findings are similar to those described in other studies (9,11). A study was done in Brazil (9) showed that asymptomatic blood donors seropositive for HTLV1 had more skin manifestation compared with the control group. A study was done by Okajima *et al.*, also showed that skin manifestations occurred in 76% of HTLV1 infected asymptomatic carriers and in 88% of the HAM/TSP patients (11).

The findings of the present study confirm the previous studies which reported xerosis as the main skin manifestation of HAM/TSP (4,11,12).

It was also shown in a study done by Lenzi *et al*., (4) that xerosis, palmar erythema, and cutaneous candidiasis were significantly associated with HAM/TSP. Although in the present study only xerosis was associated with HAM/TSP compared with the HTLV1 negative control group (*P*=0.000), it was more common in the patients who had HAM/TSP for more than 10 years (*P*=0.011). So, it could be concluded that skin involvement would increase with duration of HAM/TSP. According to our results, Skin manifestation was significantly higher in patients with moderate myelopathy compared with the patients with mild myelopathy (*P*=0.005). The authors have not found any study investigating the relationship between skin involvement and severity of myelopathy, but our results show that skin manifestation has a direct

correlation with severity of myelopathy. Females are more likely to develop HAM/TSP than males do. This is directly related to more transmission of the virus from male to female (13). Also, our results showed a high prevalence of xerosis among the female patients with HAM/TSP compared with the males.

A previous study (14) indicated that HAM/TSP patients had autoimmune disturbances with predominant sympathetic nervous system dysfunction. Other studies identified HTLV1 in the skin cells(including epithelial cells of sweat glands)of HTLV1 infected patients,in addition to their lymphocytes (9,15). Because of these findings, it is not clear that skin manifestations in HAM/TSP are the result of the hypohidrosis secondary to the autonomic nervous system dysfunction or the direct result of the HTLV1 infected cells in the skin.

The results of this study suggest that skin manifestations such as xerosis have a significant association with HAM/TSP. Although more studies are needed to reflect the HTLV1 infection associated skin manifestation among HTLV1 infected and HAM/TSP patients, this finding could be useful in the clinical setting of patients with HTLV1 infection and HAM/TSP in the endemic areas and may represent a clinical warning sign for the early diagnosis of this infection.

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References

1. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-I infection and associated diseases. Oncogene 2005;24:6058-68.
2. Matsuoka M. Human T-cell leukemia virus type I and adult T-cell leukemia. Oncogene 2003;22:5131-40.
3. LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. Lancet 1990;336:1345-7.
4. Lenzi ME, Cuzzi-Maya T, Oliveira AL, Andrada-Serpa MJ, Araújo AQ. Dermatological findings of human T lymphotropic virus type 1 (HTLV-I)-associated myelopathy/tropical spastic paraparesis. Clin Infect Dis 2003;36:507-13.
5. Blas M, Bravo F, Castillo W, Castillo WJ, Ballona R, Navarro P, et al. Norwegian scabies in Peru: the impact of human T cell lymphotropic virus type I infection. Am J Trop Med Hyg 2005;72:855-7.
6. Tokura Y, Sawada Y, Shimauchi T. Skin manifestations of adult T-cell leukemia/lymphoma: clinical, cytological and immunological features. J Dermatol 2014;41:19-25.
7. Rafatpanah H, Hedayati-Moghaddam MR, Fathimoghadam F, Bidkhori HR, Shamsian SK, Ahmadi S, et al. High prevalence of HTLV-I infection in Mashhad, Northeast Iran: a population-based seroepidemiology survey. J Clin Virol 2011;52:172-6.
8. Matsuzaki T, Nakagawa M, Nagai M, Usuku K, Higuchi I, Arimura K, et al. HTLV-I proviral load correlates with progression of motor disability in HAM/TSP: analysis of 239 HAM/TSP patients including 64 patients followed up for 10 years. J Neurovirol 2001;7:228-34.
9. Gonçalves DU, Guedes AC, Proietti AB, Martins ML, Proietti FA, Lambertucci JR, et al. Dermatologic lesions in asymptomatic blood donors seropositive for human T cell lymphotropic virus type-1. Am J Trop Med Hyg 2003;68:562-5.
10. Hanchard B. Outcomes of early life exposure to human T cell lymphotropic virus type 1. Clin Infect Dis 2005;41:542-3.
11. Okajima R, Oliveira AC, Smid J, Casseb J, Sanches JA Jr. High prevalence of skin disorders among HTLV-1 infected individuals independent of clinical status. PLoS Negl Trop Dis 2013;7:e2546.
12. Bittencourt AL, de Oliveira Mde F. Cutaneous manifestations associated with HTLV-1 infection. Int J Dermatol 2010;49:1099-110.
13. Roucoux DF, Wang B, Smith D, Nass CC, Smith J, Hutching ST, et al. A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. J Infect Dis 2005;191:1490-7.
14. Alamy AH, Menezes FB, Leite AC, Nascimento OM, Araújo AQ. Dysautonomia in human T-cell lymphotrophic virus type I-associated myelopathy/tropical spastic paraparesis. Ann Neurol 2001;50:681-5.
15. Setoyama M, Kerdel FA, Elgart G, Kanzaki T, Byrnes JJ. Detection of HTLV-1 by polymerase chain reaction in situ hybridization in adult T-cell leukemia/lymphoma. Am J Pathol 1998;152:683-9.