Published in final edited form as:

Int J Dermatol. 2014 September ; 53(9): 1098–1102. doi:10.1111/ijd.12170.

Dermatological Manifestations of Individuals Infected with Human T-cell Lymphotropic Virus type 1

Lorena Dantas, MD¹, Eduardo Netto, MD, PhD¹, Marshall Glesby, MD, PhD², Edgar Carvalho, MD, PhD³, and Paulo Machado, MD, PhD³

¹Federal University of Bahia (UFBA), Brazil.

²Department of Medicine, Weill Cornell Medical College, New York, USA.

³Immunology Service, Federal University of Bahia (UFBA), Brazil.

Abstract

Background—Human T-cell lymphotropic virus - type 1 (HTLV-1) is associated with specific manifestations such as adult T-cell lymphoma/leukemia (ATLL), HTLV-1-associated myelopathy / tropical spastic paraparesis (HAM/TSP), HTLV-1-associated uveitis and infective dermatitis associated with HTLV-1 (IDH). Although ATLL and IDH are considered specific manifestations of HTLV-1 infection, several dermatological manifestations have been described in HTLV-1-infected patients.

Methods—A prevalence study was conducted between 2008 and 2010 with two groups of individuals, 179 HTLV-1 seropositive (positive ELISA and positive Western Blot) and 193 seronegative individuals (ELISA negative). The subjects were selected at a random basis and evaluated using a questionnaire to obtain epidemiological and clinical data. A physical examination was performed to verify the presence of skin lesions.

Results—Superficial mycoses were found in 54 HTLV-1-positive subjects (30.2%) and in 26 (13.5%) of the seronegative group ($p < 0.001$). Xerosis was found in 39.1% of HTLV-1 infected subjects and in 9.3% of seronegative controls ($p < 0.001$). Ichthyosis was diagnosed in 9 HTLV-1 positive cases (5%) whereas absent in the control group ($p = 0.001$). A seborrheic dermatitis diagnosis was made in 43 HTLV-1 infected subjects (24%) and in 24 seronegative controls (12.4%) ($p = 0.004$). Furthermore, the dermatological manifestations were more intense in the HTLV-1 group.

Conclusions—Several dermatological manifestations are more common and more severe in HTLV-1 subjects. The presence of these manifestations in an endemic area for HTLV-1 infection may be a clue for the investigation of this infection.

Correspondence: Paulo Machado, MD, PhD., Immunology Service, Federal University of Bahia (UFBA), Brazil, CEP: 40 110, Tel: 55 71 32377353. prlmachado@uol.com.br.

A study conducted at the Federal University of Bahia (UFBA), Brazil.

Conflicts of interest: None.

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) was first isolated in 1980 from a patient with skin manifestations: adult T-cell lymphoma/leukemia (ATLL)¹. Later, HTLV-1-associated myelopathy / tropical spastic paraparesis (HAM/TSP) and HTLV-associated uveitis were described^{2,3}. Nevertheless, the majority of HTLV-1 carriers are considered to be asymptomatic and little is known about the spectrum of diseases that may be associated with this virus⁴. Recent studies conducted in the city of Salvador, Bahia, Brazil showed a higher frequency and diversity of clinical manifestations associated with HTLV-1^{5,6}. The presence of HTLV-1 has been documented in ATLL skin lesions and in skin lesions of otherwise asymptomatic carriers, suggesting that the skin may be the organ most affected by this virus^{7,8}. Another dermatitis specifically associated with HTLV-1 is infective dermatitis (IDH), a severe and recurrent form of childhood eczema that was initially described in 1966 by Sweet in Jamaica and characterized as being directly associated with the viral infection by La Grenade in 1990^{9,10}. Nonetheless, many skin conditions have been documented in ATLL and HAM/TSP, and several infectious or inflammatory dermatoses are currently being found in otherwise asymptomatic HTLV-1 carriers^{7,8,11,12}. These data suggest that the skin as a target organ of HTLV-1 may manifest clinical signs that could be identified as an alert to the presence of the virus in individuals considered asymptomatic. In regions in which the prevalence of HTLV-1 is high, the recognition of these manifestations may warn the clinician to investigate for the presence of this viral infection.

The objective of this study was to determine the prevalence of skin lesions in HTLV-1-infected patients at the multidisciplinary HTLV-1 outpatient clinic at the Hospital Universitário Prof. Edgar Santos of the Federal University of Bahia, Salvador, Bahia, Brazil, and to compare them with seronegative individuals recruited at the state blood bank (STS). This study was approved by the Institutional Review Board of the Federal University of Bahia. All participants signed an informed consent form.

Materials and Methods

A descriptive and prevalence study was conducted between October 2008 and September 2010 to determine the frequency and severity of abnormal skin manifestations present in HTLV-1 infected patients and to compare them with seronegative individuals recruited at STS in Salvador, Bahia, Brazil. Donors from STS were selected as the control group because the majority of HTLV-1 infected outpatients were diagnosed at the time of attempted blood donation and referred to the HTLV-1 clinic for management.

HTLV-1 seropositive group

A total of 179 patients were randomly selected from patients attending scheduled appointments at the multidisciplinary HTLV-1 clinic. Inclusion criteria consisted of positive serology for HTLV-1, confirmed by Western Blot, and age over 18 years.

All subjects were administered a questionnaire and underwent a dermatological examination irrespective of their clinical complaints as detailed below. HAM/TSP patients were diagnosed according to established criteria¹³.

HTLV-1 seronegative group

The control group consisted of 193 blood donors from STS that had been screened for HTLV-1 and found to be seronegative (ELISA-negative). These individuals were randomly selected for inclusion in the study after having donated blood. After signing the informed consent form, they answered the same questionnaire administered to the HTLV-1-positive patients that underwent dermatological examination.

Dermatological evaluation

Dermatological evaluation included complete examination of participants' skin, hair, nails and mucosa, in accordance with the protocol and irrespective of whether the individual had made any dermatological complaints. Dermatological evaluation sought to establish any abnormal skin condition. Examination included the description and location of any neoplastic or non-neoplastic skin lesions. Additionally, the extent to which the patient was affected was characterized semi-quantitatively. All the individuals were examined by the same dermatologist (Lorena Dantas, MD).

Evaluation questionnaire

The evaluation questionnaire was designed to obtain demographic and clinical data including the patient's gender, age, place of residence, education level, ethnicity and history of any breastfeeding, blood transfusion, tattoos and/or injectable drug use, as well as diagnosis of any other diseases associated or not associated with HTLV-1. The individual was questioned regarding his/her use of medication and co-morbidities as well as dermatological complaints.

Statistical analysis

Quantitative and categorical data were summarized in frequency tables. For the analysis of the quantitative data, means, medians and standard deviations were calculated. Pearson's chi-square test or Fisher's exact test was used to compare categorical data. In the analysis of the quantitative data, Student's t-test was used whenever the distribution of variables was normal. Univariate logistic regression was used to calculate odds ratios and 95% confidence intervals for the associations between specific dermatosis and patient groups (HTLV-1 versus seronegative controls). Multivariate logistic regression was used to adjust for potential confounding demographic factors. Jonckheere-Terpstra test for trend was used to compare the degree of intensity of specific dermatosis between the patient groups. Data were analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) and Stata (version 10, StatCorp, College Station, TX). The significance level was defined as $P < 0.05$.

Results

The age, gender, education level, and co-morbidities from the 372 individuals included in the study are shown in Table 1. From the 372 cases studied, 193 (51.9%) belonged to the HTLV-1-seronegative group and 179 (48.1%) to the HTLV-1-seropositive group. The mean age of the individuals in the HTLV-1-seropositive group was higher (52.2 ± 17 years) than that of the individuals in the seronegative group (33.6 ± 3 years). There was a greater prevalence of females in the seropositive group (64.2%) compared to the seronegative group

(36.3%). Education level was lower in the HTLV-1-positive group, although evaluation of family income showed no statistically significant differences between the two groups (data not shown). Dermatological complaints were found in 39% of HTLV-1 subjects and in 6% of the seronegative individuals. Eleven individuals (6.1%) were found to have diabetes mellitus, 10 in the seropositive group and one in the seronegative group ($p=0.004$). In the HTLV-1 group there were thirty-nine HAM/TSP patients and the remaining 140 patients were asymptomatic.

Table 2 shows the main dermatological findings in HTLV-1 carriers and seronegative subjects. Xerosis and superficial mycosis were the most prevalent skin diseases, found in 39% and 30% of HTLV-1 carriers compared to 9% and 13.5% in the seronegative group respectively ($p<0.001$). The diagnosis of superficial mycosis included pityriasis versicolor, onychomycosis, candidiasis and dermatophytosis. When the presence of pityriasis versicolor was evaluated alone, we found a higher prevalence in the HTLV-1 group ($p=0.01$). However, statistical significance was lost when the group of superficial mycoses was divided into subgroups of dermatophytosis, onychomycosis and candidiasis ($p>0.05$), or when adjusted for gender and age.

Seborrheic dermatitis (SD) was also a common dermatologic diagnosis with a higher prevalence in the HTLV-1 seropositive group and associated with the highest adjusted odds ratio (table 2). Acquired ichthyosis was found in 9 (5%) of the seropositive patients and in none of the individuals in the control group ($p=0.002$).

Two individuals had already been diagnosed with ATLL at the time of evaluation and both were in treatment for the disease and currently being followed-up by the hematology and dermatology teams at this institute. No case of ATLL or IDH were diagnosed during the study.

Patients with diabetes and HTLV-1 infection presented with superficial mycoses (5 cases), xerosis (3 cases) and ichthyosis (1 case), while only one case of superficial mycosis was diagnosed in a seronegative diabetic patient. In the HTLV-1-seropositive group, only two individuals were also HIV-positive. Only one had skin lesions which consisted of superficial mycosis (pityriasis versicolor).

Table 3 shows that patients with HAM-TSP had a higher prevalence of superficial mycosis, SD and xerosis ($p=0.0004$) when compared with asymptomatic HTLV-1 carriers. The prevalence of ichthyosis was the same in HAM/TSP patients as in asymptomatic carriers.

Evaluation of the intensity of the dermatological alterations showed a higher degree of severity expressed by a greater area affected by pityriasis versicolor, SD and xerosis in the seropositive group compared to the seronegative group. Onychomycosis in more than three digits was documented only in the HTLV-1 infected subjects (Table 4).

Discussion

Although HTLV-1 is considered to cause disease in a minority of infected subjects, there are recent data showing that most HTLV-1 carriers are not asymptomatic and may present

several symptoms and associated diseases^{5,6}, including cutaneous manifestations^{11,12,14,15}. The high frequency of cutaneous complains and manifestations in the HTLV-1 group found in our study varied widely and are discussed below.

According to Gonçalves et al. (2003), the prevalence of dermatophytosis in asymptomatic HTLV-1 carriers is the highest of all the dermatological lesions, affecting up to 34.4% of patients¹¹. In the present study, dermatophytosis was the least common superficial mycoses, found only in 7.8% of the HTLV-1 subjects.

Although superficial mycoses were found in 50% of the HTLV-1 patients with diabetes, the exclusion of these five patients from the comparative analysis of seropositive and seronegative individuals did not change the higher frequency of this diagnosis in the HTLV-1-positive group.

The high frequency of SD in HTLV-1-positive patients has also been described in the literature^{11,14}. The prevalence of SD in the general population ranges from 1 to 5% in different studies, with prevalence being higher in males¹⁵. Our study found a SD prevalence of 24% in the asymptomatic seropositive individuals, much higher than the 6.3% reported before¹¹. We have also found a higher severity degree of SD in the HTLV-1 carriers, as well as a higher SD prevalence in the HAM-TSP patients. In Jamaican children the HTLV-1 provirus load was higher in those who developed SD¹⁶, showing the importance of SD as a skin manifestation associated with HTLV-1 infection.

Xerosis and its more severe form, acquired ichthyosis, are the manifestations most commonly described in patients with HAM-TSP, occurring in 66.7% of cases¹⁷, and with greater intensity seen in advanced cases of myelopathy¹⁸. Acquired ichthyosis has been described in 7% of healthy HTLV-1 carriers and also in patients with HAM/TSP^{11,18}.

We have also found a higher prevalence of these manifestations in HTLV-1 carriers and HAM-TSP patients. The fact that acquired ichthyosis was found both in asymptomatic carriers and in patients with HAM/TSP but not in controls suggests that in regions that are endemic for HTLV-1 such as the city of Salvador, Bahia, Brazil, the presence of this virus should be investigated in every case of acquired ichthyosis. Furthermore, as a higher degree of xerosis was correlated with a greater neurological disability in HAM/TSP patients¹⁸, a finding of acquired ichthyosis or severe xerosis in seropositive patients should serve as an alert for the clinician regarding the possibility of future progression to HAM/TSP.

Although scabies and herpes zoster were diagnosed only in the HTLV-1-seropositive group, no cases of crusted scabies or severe herpes zoster were found.

An important finding was related to the presence of more extensive cutaneous involvement in the seropositive group when compared to the seronegative controls. For instance, moderate or extensive pityriasis versicolor was found in 7 individuals in the seropositive group and in none of the control group. Likewise, it was only in the HTLV-1-positive group that individuals with three or more digits affected by onychomycosis were found. The evaluation of the severity of SD showed that 11 patients in the HTLV-1-positive group had moderate or severe SD compared to 1 seronegative subject with moderate involvement.

Similarly, moderate or severe forms of xerosis were found in 44.2% of HTLV-1 carriers compared to 11.8% in the seronegative group (Table 3). These data suggests a role for HTLV-1 in the clinical expression of these dermatoses, but further studies need be done to clarify this intriguing question.

Our study shows that several skin diseases are more common and more severe in HTLV-1 subjects. Although these skin manifestations are not specific for HTLV-1 infection, our data underlies the concept that dermatological diseases may represent signs of internal diseases. In an endemic area for HTLV- 1 the clinician should be aware of the importance of a dermatological exam and be alerted by the presence of these manifestations as a clue for the diagnosis of a “silent” HTLV-1 infection.

Acknowledgments

This study was supported by the National Research Council (CNPq) and the Bahia State Foundation for the Support of Research (FAPESB). EMC is a senior CNPq investigator. MJG was supported in part by NIH/NIAID K24 AI078884.

References

- Poiesz BJ, Ruscetti FW, Gazder AF, et al. Detection and isolation of type C retrovirus particles from fresh and cultered lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A*. 1980; 77:7415–7419. [PubMed: 6261256]
- Román GC, Osame M. Identity of HTLV-I-associated tropical spastic paraparesis and HTLV-I-associated myelopathy. *Lancet*. 1988; 1:651. [PubMed: 2894583]
- Mochizuki M, Watanabe T, Yamaguchi K, et al. Uveitis associated with human T-cell lymphotropic virus type I. *Am J Ophthalmol*. 1992; 114:123–129. [PubMed: 1642286]
- Verdonck K, Gonzalez E, Van Dooren S, et al. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. *Lancet Infect Dis*. 2007; 7:266–281. [PubMed: 17376384]
- Caskey MF, Morgan DJ, Porto AF, et al. Clinical manifestations associated with HTLV type I infection: a cross-sectional study. *AIDS Res Hum Retroviruses*. 2007; 23:365–371. [PubMed: 17411369]
- Poetker SK, Porto AF, Giozza SP, et al. Clinical manifestations in individuals with recent diagnosis of HTLV type I infection. *J Clin Virol*. 2011; 5:54–58. [PubMed: 21388871]
- Oshima K. Pathological features of diseases associated with human T-cell leukemia virus type I. *Cancer Sci*. 2007; 98:772–778. [PubMed: 17388788]
- Setoyama M, Mizoguchi S, Kanzaki T. Prurigo as a clinical prodrome to adult T-cell leukemia/lymphoma. *Br J Dermatol*. 1998; 138:137–140. [PubMed: 9536237]
- Sweet RD. A pattern of eczema in Jamaica. *Br J Dermatol*. 1996; 78:93–100. [PubMed: 5907441]
- La Grenade L, Hanchard B, Fletcher V, et al. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. *Lancet*. 1990; 336:1345–1347. [PubMed: 1978165]
- Gonçalves DU, Guedes AC, Proietti AB, et al. Dermatology lesions in asymptomatic blood donors seropositive for human T cell lymphotropic virus type-1. *Am J Trop Med Hyg*. 2003; 68:562–565. [PubMed: 12812346]
- Nobre V, Guedes AC, Proietti FA, et al. Lesões dermatológicas em pacientes infectados pelo vírus linfotrópico humano de células T do tipo 1 (HTLV-1). *Rev Bras Med Trop*. 2005; 38:43–52.
- Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. *Lancet*. 1986; 1:1031–1032. [PubMed: 2871307]
- Maloney EM, Wiktor SZ, Palmer P, et al. A cohort study of health effects of human T-cell lymphotropic virus type I infection in Jamaican children. *Pediatrics*. 2003; 112:136–142.
- Faergemann J. Management of Seborrheic Dermatitis and Pityriasis Versicolor. *Am J Clin Dermatol*. 2000; 1:75–80. [PubMed: 11702314]

16. Maloney EM, Nagai M, Hisada M, et al. Prediagnostic human T lymphotropic virus type I provirus loads were highest in Jamaican children who developed seborrheic dermatitis and severe anemia. *J Infect Dis.* 2004; 189:41–45. [PubMed: 14702151]
17. Hashiguchi, T.; Osame, M.; Arimura, K. Skin manifestations in HTLV-I associated myelopathy (HAM): xerosis and erythema. In: Román, CG.; Vernant, JC.; Osame, M., editors. *HTLV-I and the nervous system*. New York (NY): Alan R. Liss, Inc; 1989. p. 443-448.
18. Lenzi MER, Cuzzi-Maya T, Oliveira ALA, et al. Dermatological findings of human T lymphotropic virus type 1 (HTLV-I)-associated myelopathy/tropical spastic paraparesis. *Clin Infect Dis.* 2003; 36:507. [PubMed: 12567310]

Table 1

Socio-demographic data and co-morbidities found in the HTLV-1-positive patients and the seronegative controls evaluated in Salvador, Bahia, Brazil.

	Seropositive (n=179) n(%)	Seronegative (n=193) n(%)	p-value*
Gender			< 0.001
Male	64 (35.8)	123 (63.7)	
Female	115 (64.2)	70 (36.3)	
Age range (year)			< 0.001
18–29	6 (3.4)	78 (40.4)	
30–49	68 (38.0)	97 (50.3)	
50 +	105 (58.7)	18 (9.3)	
Education level			< 0.001
Illiterate	10 (5.6)	0 (0)	
Primary	83 (46.4)	49 (27.4)	
Secondary	75 (41.9)	92 (51.4)	
Tertiary	11 (6.1)	52 (29.1)	
Co-morbidities			< 0.001
Arterial hypertension	66 (36.9)	6 (3.1)	
Hypothyroidism	6 (3.4)	0 (0)	
Diabetes Mellitus	10 (5.6)	1 (0.5)	
Tuberculosis	9 (5.0)	0 (0)	
HIV	2 (1.4)	0 (0)	
Hepatitis B	11 (7.9)	0 (0)	
Hepatitis C	13 (9.3)	0 (0)	

*
Chi-square test

Distribution of the dermatological findings found in the HTLV-1-positive patients and the seronegative controls evaluated in Salvador, Bahia, Brazil, 2008–2010.

Table 2

Cutaneous disease (Prevalence)	Seropositive (n=179) n(%)	Seronegative (n=193) n(%)	OR	95% CI	P-value	aOR*	95% CI	P-value
Xerosis	70 (39.1)	18 (9.3)	6.24	3.53–11.0	< 0.001	3.45	1.71–6.96	0.001
Superficial mycosis	54 (30.2)	26 (13.5)	2.77	1.65–4.68	< 0.001	1.80	0.92–3.55	0.088
Seborrheic dermatitis	43 (24.0)	24 (12.4)	2.23	1.29–3.85	0.004	4.02	1.92–8.39	<0.001
Acquired ichthyosis	9 (5.0)	0	--	--	0.001**			
Scabies	4 (2.2)	0	--	--	0.053**			
Herpes Zoster	2 (1.1)	0	--	--	0.23**			
ATLL***	2 (1.1)	0	--	--	0.23**			

* aOR = adjusted odds ratio from multiple logistic regression model adjusting for gender and age

** Fisher's exact test

*** Adult T-cell lymphoma/leukemia

Table 3

Dermatological findings in the HTLV-1 carriers according to clinical status.

Cutaneous disease	HAM/ TSP (n = 39)	Asymptomatic n = 140)	P-value*
Xerosis	25 (64%)	45 (32%)	0.0004
Superficial mycosis	16 (41%)	38 (27%)	0.11
Seborrheic dermatitis	14 (36%)	29 (21%)	0.06
Ichthyosis	2 (5%)	7 (5%)	1.0

* Fisher's exact test.

Table 4

Degree of intensity of cutaneous diseases in HTLV-1 seropositive and seronegative individuals.

Cutaneous disease	Seropositive (n = 179)	Seronegative (n = 193)	P-value *
Pityriasis Versicolor			0.01
Localized (1 region)	14	9	
Moderate (2–3 regions)	5	0	
Extensive (4 regions)	2	0	
Onychomycosis (hands and feet)			0.07
1–2 digits	17	11	
3–5 digits	3	0	
6 digits	2	0	
Seborrheic dermatitis			0.002
Localized	32	23	
(face or scalp)			
Moderate	10	1	
(face and scalp)			
Extensive	1	0	
(more than the face and scalp)			
Xerosis			< 0.001
Mild	39	15	
(mild, lower or upper limbs)			
Moderate	14	2	
(mild, lower and upper limbs)			
Severe	17	0	
(intense and/or diffuse)			

* Jonckheere-Terpstra test