

ORIGINAL ARTICLE

Oral manifestations of human T-cell lymphotropic virus infection in adult patients from Brazil

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OBJECTIVE: Human T-cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus discovered and its pathogenesis is related to T cells infection. This study aimed to verify the presence of oral manifestations in a Brazilian population of patients who was seropositive for HTLV, and identify risk factors for oral manifestations.

SUBJECTS AND METHODS: An assessment was made of 139 patients at the Emilio Ribas Institute of Infectious Diseases.

RESULTS: A total of 112 (80.5%) patients were HTLV-1, 26 (18.7%) were HTLV-2+. About 35.2% of patients had myelopathy/tropical spastic paraparesis (HAM/TSP), with 48 of them being HTLV-1+ and one patient was seropositive for HTLV-1 and -2. The most common oral manifestations were: xerostomia (26.8%), candidiasis (20.8%), fissured tongue (17.9%), and loss of tongue papillae (10.0%). A multivariate logistic regression analysis showed that HAM/TSP is an independent risk factor for xerostomia ($P = 0.02$). The patients who were HAM/TSP+ were three times more likely to develop xerostomia when compared with patients without HAM/TSP (odds ratio = 2.69, 95% confidence interval = 1.17–6.17).

CONCLUSION: Despite the fact that the findings of this study suggest a relationship between xerostomia and HAM/TSP, more studies should be developed to show what the association would be between xerostomia presented by HTLV patients and pathogenesis of the virus.

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Keywords: human T-cell lymphotropic virus; oral manifestations; xerostomia; HTLV-associated myelopathy/tropical spastic paraparesis

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus to be identified, and was isolated for the first time in 1980 (Poiesz *et al*, 1980; Bangham, 2000). HTLV-2 was discovered in 1982 (Feuer and Green, 2005) and, recently, types 3 and 4 have been identified (Calattini *et al*, 2005; Wolfe *et al*, 2005).

The HTLV-1 is the most prevalent and most studied type. It is estimated that 15–20 million people are currently infected with the virus, with endemic regions in southwestern Japan, the Caribbean, Iran, some Latin American countries and central and southern regions of Africa. HTLV-2 is more common among indigenous tribes of Central, North and South America (Murphy *et al*, 2005; Proietti *et al*, 2005). Types 3 and 4 were identified only in patients from the African continent (Calattini *et al*, 2005; Wolfe *et al*, 2005).

In Brazil, it is estimated that there are about 2.5 million patients infected with HTLV-1, making it the country with the largest absolute number of cases (Carneiro-Proietti *et al*, 2002).

The HTLV-1 has been definitively linked to two distinct types of incurable diseases: HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATLL), as well as autoimmune, infectious and other types of neoplasias (Verdonck *et al*, 2007). HAM/TSP is an inflammatory demyelinating disease that involves the production of autoantibodies against antigens of HTLV-1 and ATLL, a malignant neoplasia of activated post-thymic pleomorphic T lymphocytes (Matutes, 2007).

A few studies to identify oral alterations in HTLV-seropositive patients, except for a few case reports of ATLL in the oral cavity (Segami *et al*, 1990; Albuquerque *et al*, 2005).

On the other hand, several studies have associated HTLV with Sjögren's syndrome (SS) or an SS-like condition (Terada *et al*, 1994; Nakamura *et al*, 1997, 2000; Izumi *et al*, 1999; Merle *et al*, 1999, 2002), thus leading to the hypothesis that a dry mouth sensation,

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named xerostomia, one of the main characteristics of this syndrome (Kassan and Moutsopoulos, 2004), may be a clinically identifiable consequence of HAM/TSP (Caskey *et al*, 2007; Giozza *et al*, 2008). It is worth highlighting that xerostomia, which is usually caused by hypofunction of the salivary glands, can be caused by several factors such as systemic diseases (diabetes and kidney disease), radiation, use of medications, autoimmune diseases and some viral infections (Bergdahl, 2000; Thomson *et al*, 2000; Scully and Bagan, 2004; Berk, 2008), and these factors may be superimposed in HTLV-1-infected subjects.

Objective

This study aimed to verify the presence of oral manifestations in a Brazilian population of patients who was seropositive for HTLV, and identify risk factors for oral manifestations.

Subjects and methods

The design of this study was approved by the Research Ethics Committee of the Emilio Ribas Institute of Infectious Diseases. All patients signed a written informed consent form.

Dental assessments were carried out by one trained and calibrated dental surgeon and consisted of medical history and physical examination, using a specific data collection form. The following data were collected from 139 patients who were seropositive for the virus: CD4, CD8 and viral load count (VLC), presence of comorbidities (other diseases or systemic infections), presence of HAM/TSP, smoking, drinking and use of medicines and illicit drugs. The diagnosis of oral lesions was made on the basis of clinical presentation and was confirmed by direct microscopy if necessary.

Statistical analysis was carried out using the Statistical Package for Social Sciences (v16.0) software. For comparison between the qualitative variables, Fisher's exact test was used for 2×2 tables and Monte-Carlo simulation was used to estimate the *P*-value in 3×2 tables. The Kruskal–Wallis test was used to compare quantitative data. The significance level was set as 0.05 or 5%. Multivariate logistic regression was also used to identify independent risk factors for the manifestation of oral alterations.

Results

Of 139 HTLV patients evaluated, 86 (61.9%) were female and 53 (38.1%) were male and the majority ($n = 85$, 61.1%) were between the third and fourth decade of life. The use of tobacco was identified in 36 patients (25.8%), nine (6.4%) used illicit drugs (marijuana and cocaine) and six (4.3%) were alcohol drinkers.

A total of 112 (80.5%) were seropositive for HTLV-1; of these, 64 (57.1%) were asymptomatic and 48 (42.8%) had HAM/TSP. Seropositivity for HTLV-2 was identified in 26 (18.7%) patients. None of these patients had

a diagnosis of HAM/TSP. Only one (0.7%) patient was seropositive for both viral types, and also presented HAM/TSP.

The CD4, CD8 and VLC were present in 111, 104, and 122 patients, respectively. The CD4 counts ranged from 75 to 3898 with a mean of 1014.51 (s.d. = 536.96) and CD8 ranged from 54 to 2606 with a mean of 680 (s.d. = 372.70). The HTLV-1 proviral load was 0–7451 with a mean of 358.98 (s.d. = 915.96).

Many seropositive patients also had other systemic diseases (comorbidities). In 87 (62.5%) patients, the following conditions were identified: diabetes (10), liver diseases (47), kidney diseases (18), heart diseases (11), hypertension (29), gastrointestinal diseases (17), skin diseases (27), anemia (23), human immunodeficiency virus (HIV; 32), hepatitis-B virus (HBV; 6), and hepatitis-B virus (HCV; 42).

As a result of the presence of comorbidities, and the need for treatment for the manifestations of HAM/TSP, 97 patients (69.7%) regularly used medications. To treat HIV infection 29 patients (20.8%) used antiretrovirals and to HCV infection five (3.59%) used ribavirin plus interferon. To control the clinical manifestations of HAM/TSP, 28 patients (20.14%) used baclofen, 20 (14.38%) amitriptyline, 14 (10.07%) anti-inflammatories, and 11 (7.91%) analgesics. Other medications used by HTLV+ patients were anti-hypertensives ($n = 21$; 15.10%), anxiolytics ($n = 14$; 10.07%), anticonvulsants ($n = 3$; 2.15%) and antidepressants ($n = 2$; 1.43%).

Of the 139 patients evaluated, 74 (53.23%) had oral cavity alterations: 26.8% had xerostomia ($n = 36$), 20.8% candidiasis ($n = 29$), 17.9% fissured tongue ($n = 25$), 10.0% loss of tongue papillae ($n = 14$), 8.6% angular cheilitis ($n = 12$), 5% had Fordyce granules ($n = 7$), 2.8% gingivitis ($n = 4$), 2.8% recurrent oral ulcer disease ($n = 4$), 2.1% herpes simplex ($n = 3$), 1.4% inflammatory fibrous hyperplasia ($n = 2$), 1.4% nevus ($n = 2$), and 0.7% burning mouth syndrome ($n = 1$).

The presence of oral manifestations was more frequent in HTLV-1-infected subjects (80.6%); comorbidities (57.5%); with medication use (69.7%), and those with HAM/TSP diagnosis (45.2%). There was no statistical difference between age and VLC of individuals with different oral changes ($P < 0.05$). Table 1 shows the studied variables. HAM/TSP patients had a higher frequency of xerostomia (43.5%) compared with asymptomatic HTLV carriers (18.4%) ($P = 0.004$). Patients who used medication regularly had a higher frequency of xerostomia (33%) compared with patients who did not take medication (11.9%; $P = 0.011$; Table 2).

The patients with candidiasis had lower CD4 levels compared with patients who did not have candidiasis ($P = 0.032$). When the CD4 level was categorized into three groups (CD4 < 200 cells/mm³, CD4 > 200 < 500, CD4 > 500) it was observed that patients with CD4 levels lower than 500 were approximately seven times more likely to develop candidiasis compared with those with CD4 > 500 cells/mm³ [odds ratio (OR) = 6.60, 95% confidence interval (CI) = 1.01–43.04]. None

Table 1 Whole numbers (*N*) and frequency (%) of the studied variables in the sample

Variables	Presence	
	Yes	No
Xerostomia, <i>n</i> (%)	36 (26.8)	103 (73.2)
Loss of tongue papillae, <i>n</i> (%)	14 (10.0)	125 (90.0)
Fissured tongue, <i>n</i> (%)	25 (17.9)	114 (82.1)
Candidiasis, <i>n</i> (%)	29 (20.8)	110 (79.2)
HTLV-1, <i>n</i> (%)	113 (81.2)	26 (18.8)
HTLV-2, <i>n</i> (%)	26 (18.8)	113 (81.2)
HAM/TSP, <i>n</i> (%)	49 (43.3)	90 (56.6)
Medications, <i>n</i> (%)	96 (69.0)	43 (31.0)
Comorbidities, <i>n</i> (%)	80 (57.5)	59 (42.5)
Tobacco use, <i>n</i> (%)	36 (25.8)	103 (74.2)
Alcohol use, <i>n</i> (%)	6 (4.3)	133 (95.7)
Illicit drugs, <i>n</i> (%)	9 (6.4)	130 (93.6)

HTLV, human T-cell lymphotropic virus; TSP, tropical spastic paraparesis.

of the other variables had significant differences on oral alterations ($P > 0.05$) (Table 2).

A multivariate logistic regression to identify independent risk factors was carried out including only those variables that presented $P < 0.05$ in univariate analysis. Only the presence of HAM/TSP was an independent risk factor for the development of xerostomia ($P = 0.02$). In fact, HAM/TSP cases are approximately three times more likely to develop xerostomia when compared with HTLV-1-asymptomatic carriers (non-HAM/TSP), even after control for medication use (OR = 2.69, 95% CI = 1.17–6.17).

Discussion

In this study, 12 different oral alterations were identified in patients with HTLV, with the four most prevalent being of greatest interest. As the most frequent oral alterations were xerostomia, loss of tongue papillae, the

fissured tongue and candidiasis, the possible influence of the variables under study on the frequency of these conditions was evaluated.

Xerostomia was the main alteration found in the patients who were examined. There are different causes that could be pointed out as triggers of xerostomia in these patients: co-infections by HIV and HCV, which are related to the development of sialadenitis induced by lymphocytic infiltration of salivary glands (Carrozzo and Gandolfo, 2003; von Bültzingslöwen *et al*, 2007), the presence of certain systemic diseases such as diabetes, which could be responsible for the gradual replacement of glandular parenchyma by fibrous tissue causing hypertrophy of the parotid glands (von Bültzingslöwen *et al*, 2007) and the use of tobacco and various medications, particularly those used to treat depression and chronic pain (including musculoskeletal pain), which are known to cause xerostomia (Bergdahl, 2000; Thomson *et al*, 2000; Cassolato and Turnbull, 2003; Scully and Bagan, 2004; Moore and Guggenheimer, 2008). But none of these factors can be statistically related to it. On the other hand, HAM/TSP had a strong association with xerostomia.

The presence of alterations such as fissured tongue, loss of tongue papillae and candidiasis may also be co-related to xerostomia, as xerostomia may cause mucosal friability and form cracks and ulcers. Therefore, the oral tissues are more susceptible to fungal infections such as candidiasis (Cassolato and Turnbull, 2003; Eveson, 2008). In addition, because candidiasis is associated with low levels of CD4, it seems to be more a consequence of the immunosuppression caused by HIV (Kerdpon *et al*, 2004) than an oral manifestation linked to HTLV.

Despite being the first human retrovirus isolated in humans that is associated to malignancies (Poiesz *et al*, 1980), the literature still has little information on the infection by and pathogenesis of HTLV when compared with other retroviruses identified later, such as the human immunodeficiency virus. It is possible that difference in knowledge between the two viruses is linked to the fact that the virus causes disease in only 5% of infected patients and is fatal in only a few cases.

The HAM/TSP is the most prevalent clinical manifestation in these patients and can be defined as a clinical pyramidal syndrome with axomyelinic degeneration of the corticospinal tract and of the posterior column (Nakamura, 2000). It is estimated that this degeneration is caused by the strong inflammatory response to the virus, with predominance of CD4+ T cells. The CD4+ T cells infected by HTLV spontaneously produce neurotoxic pro-inflammatory cytokines, which are found in high levels in the cerebrospinal fluid and in spinal column lesions of patients with HAM/TSP (Nakamura, 2000; Goon *et al*, 2004; Shuh and Beilke, 2005).

High amounts of HTLV-1 proviral load among HAM/TSP cases can induce systemic inflammation in various organs (Furuya *et al*, 1998), causing polymyositis, arthropathies, dermatitis, uveitis, and SS (Nakamura *et al*, 1997; Verdonck *et al*, 2007).

Table 2 Comparison between the most common oral manifestations with the studied variables

	Xerostomia		LTP		FT		Candidiasis	
	P	n	P	n	P	n	P	n
Gender*	0.843	136	1.000	113	0.818	113	1.000	114
HTLV-1*	0.461	136	0.072	113	1.000	113	0.396	114
HTLV-2*	0.341	136	0.069	113	1.000	113	0.584	114
HAM/TSP*	0.004	133	0.776	110	0.818	110	0.658	111
Medications*	0.011	136	0.346	113	0.074	113	0.325	114
CD4 levels**	1.000	111	0.246	92	0.155	92	0.032	93
CD8 levels**	0.605	104	0.849	86	0.705	86	0.060	87
Comorbidities*	0.554	136	1.000	113	0.227	113	1.000	114
Tobacco use*	0.508	130	1.000	108	1.000	108	0.802	109
Alcohol use*	1.000	130	0.080	108	1.000	108	1.000	109
Illicit drugs*	1.000	129	1.000	108	0.198	108	0.406	109

LTP, loss of tongue papillae; FT, fissured tongue; HTLV, human T-cell lymphotropic virus; TSP, tropical spastic paraparesis; **P*, probability of Fisher's exact test, ***P*, probability obtained with Monte-Carlo Simulation (10 000 tables sampled). Values in bold are $P < 0.05$.

Sjögren's syndrome is particularly characterized by the accumulation of lymphocytes (predominantly CD4+ T cells) in salivary, lacrimal and other exocrine glands (Horsfall *et al*, 1989 Buckley, 2003). It is suggested, although, that the dry component of SS (xerostomia) is not caused by an irreversible structural damage of the secretory acini, but at least for some time, by a reversible functional disorder that may be linked to the neurologic control of salivary secretion (Fedele *et al*, 2008). Some studies have reported the association between SS and manifestations of the central nervous system, such as transverse myelitis (TM), arguing that the vasculitis and immune injury of the spinal column caused by reactive T cells are possible causes of TM in patients with SS (Theodoridou and Settas, 2008).

Therefore, xerostomia can be explained by two different routes: the clonal expansion would cause a high amount of CD4+ T cells that in turn could cause damage by locally infiltrating the salivary glands (Ohyaama *et al*, 1998; Sasaki *et al*, 2000), releasing pro-inflammatory cytokines which would cause vasculitis and prevent salivary flow and/or the degeneration of the nervous system itself would be involved in the decrease in salivary flow of patients.

Despite the fact that the findings of this study suggest a relationship between xerostomia and HAM/TSP, more studies should be developed to show what the association would be between xerostomia presented by HTLV patients and pathogenesis of the virus.

Author contributions

These authors contributed equally to this study.

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