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# Co-presentation of human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis and adult-onset infective dermatitis associated with HTLV-1 infection

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## Abstract

**Background** Human T-cell lymphotropic virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia/lymphoma (ATLL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), infective dermatitis associated with HTLV-1 (IDH), and various other clinical conditions. Several of these diseases can occur in association.

**Objective** Report an association of diseases related to HTLV-1 infection, occurring in an unusual age group.

**Methods** Dermatological and laboratory exams were consecutively performed in HTLV-1-infected individuals from January 2008 to July 2010 in the HTLV Outpatient Clinic at the Institute of Infectious Diseases "Emilio Ribas" in São Paulo, Brazil.

**Results** A total of 193 individuals (73 HAM/TSP and 120 asymptomatic carriers) were evaluated, three of which were associated with adult-onset IDH and HAM/TSP. In all three cases, the patients were affected by IDH after the development and progression of HAM/TSP-associated symptoms.

**Limitations** Small number of cases because of the rarity of these diseases.

**Conclusion** We draw attention to the possibility of co-presentation of adult-onset IDH in patients with a previous diagnosis of HAM/TSP, although IDH is a disease classically described in children. Thus, dermatologists should be aware of these diagnoses in areas endemic for HTLV-1 infection.

## Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia/lymphoma (ATLL)[1] and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[2] Various other clinical conditions, including uveitis, thyroiditis, arthritis, polymyositis, and infective dermatitis associated with HTLV-1 (IDH), are associated with HTLV-1 infection.[3–7] Several of these diseases, such as IDH and HAM/TSP, can occur in association.[8] However, these inflammatory diseases are generally described in individual case reports, with few studies addressing their prevalence and co-presentation in HTLV-1-infected populations.

HTLV-1-associated myelopathy/tropical spastic paraparesis is a disabling myelopathy that results in chronic spastic paraparesis, progressive proximal weakness of the lower limbs, neurogenic bladder, and back pain. Disease onset usually occurs during the fourth or fifth decade of life, with women predominantly being afflicted.[2,9,10] In HTLV-1-infected individuals, the estimated incidence of HAM/TSP ranges from 0.25% to 1% after 30–40 years of infection.[11] Several potential predisposing factors have been described, including high HTLV-1 proviral load, genetic background, high antibody titers, and routes of infection.[7,12,13]

Infective dermatitis associated with HTLV-1 was originally described in Jamaican children as relapsing and chronic eczema associated with refractory *Staphylococcus aureus* or beta-hemolytic *Streptococcus* skin infections. It involves the scalp, axilla, groin, neck, ears, eyelid margin, and paranasal skin.[14,15] According to criteria proposed by La Grenade *et al.*[16] in 1998 modified for Bittencourt and de Oliveira,[17] IDH diagnosis is based on clinical features

and positive HTLV-1 serology. The diagnostic criteria are divided into five major and seven minor criteria (Table 1). For IDH diagnosis, four of the five major criteria are required with mandatory inclusion of criteria 1, 3, and 5; to fulfill criteria 1, the involvement of at least two sites is required.[16,17] However, the association of HAM/TSP and IDH in adult HTLV-1-infected subjects remains to be established worldwide.

With more than two million HTLV-1 carriers nationwide, Brazil is considered to be endemic for HTLV-1.[18] Currently, seven cases of adult-onset IDH have been described in the literature: six in Brazil[19,20] and one in Japan;[21] of these, only one case was associated with HAM/TSP.[19] However, few reports showing the prevalence of dermatological conditions have been described in HTLV-1-infected adults. Here, we describe the clinical and laboratory features of three cases of adult-onset IDH associated with HAM/TSP.

## Patients and methods

A total of 193 HTLV-1-infected individuals were consecutively evaluated from January 2008 to July 2010 in the HTLV Outpatient Clinic at the Institute of Infectious Diseases "Emilio Ribas" (IIER). As patients, participants were given support from nurses, nutritionists, and physical therapists during follow-up. The Ethical Board of the IIER approved the protocol. Informed consent was obtained from and signed by all participants before study inclusion.

Three adult patients with HAM/TSP received an IDH diagnosis at the HTLV Outpatient Clinic at IIER in São Paulo, Brazil. Demographic and clinical dates were collected, and dermatological examinations were performed. Patients underwent laboratory tests, including HTLV-1 serologic diagnosis, T-cell proliferation assays, CD4 and CD8 counts, HTLV-1 DNA proviral load, skin culture for bacterial pathogens, and skin punch biopsies. IDH and HAM/TSP diagnoses were made according to previously established criteria.[16,17,22] Antibodies against HTLV-1/2 were detected by diagnostic enzyme-linked immunosorbent assays and confirmed by Western blot and polymerase chain reaction, techniques capable of discriminating between HTLV-1 and HTLV-2.

Peripheral blood mononuclear cell (PBMC) isolations were performed as described previously.[23] Briefly, 10 ml of peripheral blood was collected and heparinized from each patient and control subject. PBMCs were then isolated using a Ficoll-Hypaque (Pharmacia, New Jersey, NJ, USA) gradient, washed two times in sterile saline, and resuspended in RPMI 1640 (Difco, New York, NY, USA). Next, cells were pulsed with tritiated thymidine (0.5 mCi/ml, Amersham International, Little Chalfont, Buckinghamshire, UK) for 18 h before being harvested using a semiautomatic cell harvester (Flow Laboratories, London, UK) and counted in a b-counter (Beckman, Fullerton, CA, USA).[23] For each patient, the mean counts per minute of triplicate samples were calculated.

Quantitative proviral DNA levels were detected using real-time automated polymerase chain reaction; TaqMan probes were used for the *pol* gene. The albumin gene was used as the internal genomic control, and MT2 cells were used as positive control. The results are reported as copies/10,000 PBMCs; the detection limit was 10 copies.[24]

To determine the $CD4^+$ and $CD8^+$ T-cell counts, fresh whole blood specimens were collected in EDTA tubes and subjected to flow cytometry (Coulter® EPICS® XL-MCLÔ Flow Cytometer, Beckman Coulter, Beckman, Fullerton, CA, USA) after being stained with fluorochrome-conjugated monoclonal antibodies against human CD3, CD4, and CD8.

**Table 1** Criteria for diagnosis of infective dermatitis associated to human T-cell lymphotropic virus type 1

| |
|---|
| Major criteria[a] |
| 1. Eczema of scalp, axillae and groin, external ear and retroauricular areas, eyelid margin, paranasal skin and/or neck |
| 2. Chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares |
| 3. Chronic relapsing dermatitis with prompt response to appropriate therapy but prompt recurrence on withdrawal of use of antibiotics |
| 4. Usual onset in early childhood |
| 5. Human T-lymphotropic virus type 1 antibody seropositivity |
| Minor criteria |
| Positive cultures for *Staphylococcus aureus* and/or β-hemolytic streptococci from the skin or anterior nares |
| Generalized fine papular rash (in most severe cases) |
| Generalized lymphadenopathy with dermatopathic lymphadenitis |
| Anemia |
| Elevated erythrocyte sedimentation rate |
| Hyperimmunoglobulinemia (IgD and IgE) |
| Elevated CD4 count, CD8 count and CD4/CD8 ratio |

[a]Of the five major criteria, four are required for diagnosis with mandatory inclusion of 1, 3, and 5; to fulfill criteria 1, involvement of at least two of the sites is required. (Bittencourt and de Oliveira[17] modified from La Grenade *et al.*[16]).

 

## Results

In the last 14 years, 700 individuals were examined at the HTLV Outpatient Clinic at IIER; of these, 360 were infected with HTLV-1. Overall, 193 HTLV-1-infected subjects underwent consecutive dermatological examinations from January 2008 to July 2010. All patients were negative for HIV infection. A total of 73 patients had HAM/TSP, and 120 were healthy HTLV-1 asymptomatic carriers. Patients were examined by a single dermatologist, who was blinded to their HTLV serological status and clinical diagnosis.

In total, 73 patients with HAM/TSP and 120 asymptomatic patients with a mean of age of 49.4 ± 12.3 years were dermatologically evaluated. Of the patients with HAM/TSP, 55 (75%) were diagnosed with skin diseases associated with HTLV-1 (HTLV-1-associated infective dermatitis, acquired ichthyosis, xerosis, or seborrheic dermatitis). Nine (12.5%) had other skin conditions, and nine were dermatologically normal. In the asymptomatic group, 61 patients (51%) exhibited skin diseases associated with HTLV-1 infection (xerosis or seborrheic dermatitis), 37 (31%) showed no skin illness, and 22 (18%) were diagnosed with other skin diseases not usually related to HTLV-1 infection.

In accordance with clinical diagnosis, the most prevalent skin diseases in asymptomatic carriers were xerosis (51 of 120), seborrheic dermatitis (18 of 120), and onychomycosis (17 of 120). In the HAM/TSP group, seborrheic dermatitis (35 of 73), xerosis (26 of 73), and acquired ichthyosis (18 of 73) were most common.

During follow-up, three cases were diagnosed as adult-onset IDH associated with HAM/TSP according to previously established criteria. All three patients were females, with a mean age of 51.6 years, and neither had history of eczema in childhood or puberty. While the average time from HAM/TSP and IDH symptom onset were 9 and 3 years, respectively, and the average time from HAM/TSP and IDH diagnosis were 4 and 1.5 years, respectively (Table 2). One patient may have been infected via blood transfusion. The remaining two patients had no information regarding possible routes of transmission. Motor dysfunction evaluation using neurological scales demonstrated advanced HAM/TSP disease in all three patients (data not shown).

Dermatologic examinations revealed erythematous scaly lesions on the ears, face, and neck of each patient (Figs. 1–3). Axillar, groin, and popliteal fossa involvement, formation of crusts on the scalp, and papular rashes were observed in two patients (Fig. 4). Additionally, none of the patients exhibited chronic nasal discharge and/or crusting in the nostrils (Table 3).

**Table 2** Clinical and immunological parameters among adult-onset infective dermatitis associated to HTLV

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Gender | Female | Female | Female |
| Age (Years) | 44 | 65 | 46 |
| Race | Mulatto | Caucasian | Caucasian |
| Time from onset symptoms of HAM/TSP (years) | 9 | 15 | 4 |
| Time for onset diagnosis of HAM/TSP (years) | 7 | 5 | 0.5 |
| Time for onset symptoms of IDH (years) | 3 | 3 | 3 |
| Time for onset diagnosis of IDH (years) | 1 | 2 | 0.5 |
| LPA basal 3 d (cpm) | 11 966 | 11 923 | 2074 |
| $CD4^+$ (cells/$mm^3$) | 1751 | 1334 | ND |
| $CD8^+$ (cells/$mm^3$) | 621 | 1191 | ND |
| HTLV-1 DNA proviral load (copies/$10^4$ PBMC) | 6123 | 95 | ND |

HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-cell lymphotropic virus type 1; IDH, infective dermatitis associated to HTLV-1; LPA, lymphocyte proliferation assay; ND, not done; PBMC, peripheral blood mononuclear cells.

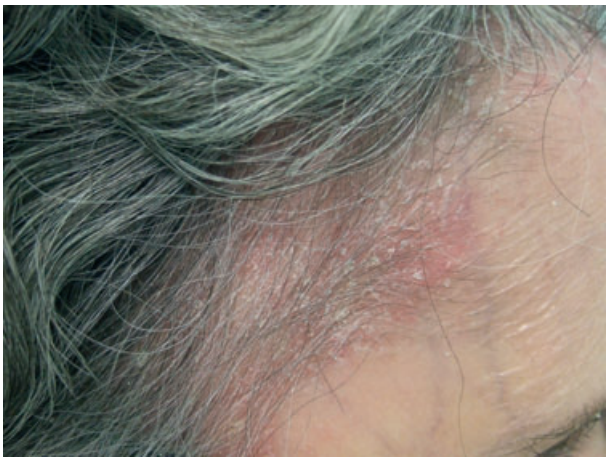

**Figure 1** Case 2. Erythematous scaly lesions on face and scalp

Skin cultures for bacterial pathogens were performed in two patients and were positive for *Staphylococcus aureus*. Patient lymphocyte proliferative responses following stimulation with mitogens (PHA and PWM) and antigens (OKT3 and CMA) as well as proviral load showed high levels in all patients. In two patients, in whom the test was performed, CD4 and CD8 counts were in the normal range. Histopathological analysis revealed superficial

 

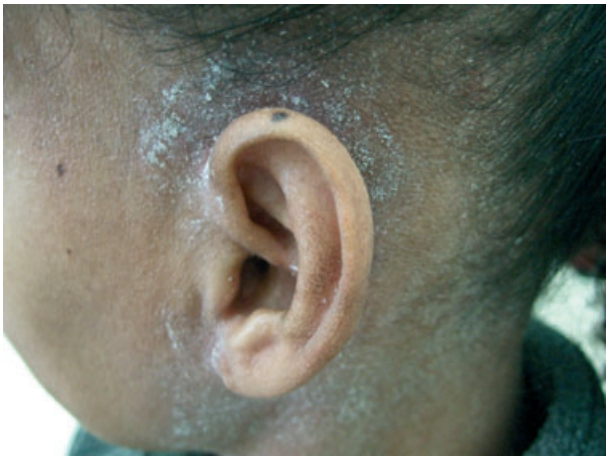

**Figure 2** Case I. Erythematous scaly lesions on scalp and retroauricular

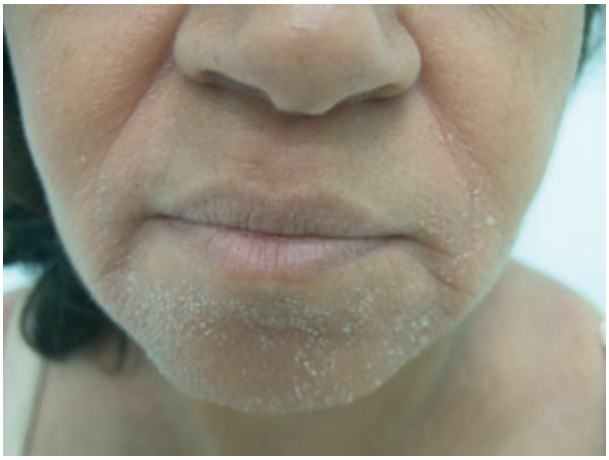

**Figure 3** Case 3. Erythematous scaly lesions on face

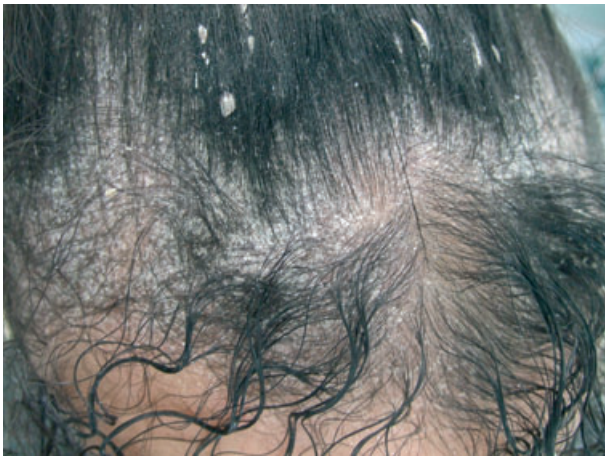

**Figure 4** Case1. Greasy and adherent scale and crusts on scalp

**Table 3** Skin manifestations and lesion distributions among adult-onset infective dermatitis associated to human T-cell lymphotropic virus type 1 infection

| Description and distribution of skin lesions | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Scalp, ears, face, and neck erythematous scaly lesions | Present | Present | Present |
| Greasy crusts on scalp and axillary, groin, and inframammary erythematous scaly lesions | Present | Present | Absent |
| Papular rashes and popliteal flexures erythematous scaly lesions | Present | Absent | Present |
| Acquired ichthyosis | Present | Present | Present |
| Chronic nasal discharge and/or crusting in the nostrils | Absent | Absent | Absent |

perivascular dermatitis in case 2 and chronic inflammatory processes with pigment incontinence in case 3.

All three patients received corticosteroid pulse therapy with methylprednisolone to treat HAM/TSP and antibiotics such as norfloxacin, ciprofloxacin, ceftriaxone, sulfamethoxazole, and trimethoprim during urinary infection episodes. Patient 1 died from sepsis following recurrent visits to the critical care unit due to neurogenic bladder caused by HAM/TSP.

## Discussion

The association between HAM/TSP and IDH has been described previously.[8,25] Classically, IDH develops in childhood, while HAM/TSP and other HTLV-1-associated diseases commonly develop in adults.[6,7,16] However, Primo *et al.*[25] identified a 30% occurrence of HAM/TSP among children previously diagnosed with IDH. To date, only seven cases of IDH have been described in adults; of these, one was associated with HAM/TSP.[19–21] In our cohort, all patients stated that neurological symptoms preceded skin lesion development. Taken together, these findings suggest that age is not a crucial factor for the identification of HAM/TSP or IDH. Thus, dermatologists and neurologists should be aware that these diseases could occur in individuals of any age.

With the exception of Jamaica, IDH is considered a rare disease in most parts of the world.[6] Although Brazil is considered endemic for HTLV-1, the distribution of HTLV-1 infections throughout the country is heterogeneous. The seroprevalence in volunteer blood donors in Brazil ranged from 3.2/1000 in São Paulo to 9.4/1000 in Bahia.[26] Thus, increased rates of IDH in children from Bahia may be related to the threefold higher number of HTLV-1-infected individuals living in the area.[25–28]

 

According to changes in the major criteria for the diagnosis of IDH,[17] chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares are now no longer considered obligatory criteria for diagnosis of IDH. The absence of these criteria does not invalidate an IDH diagnosis because these symptoms may be present intermittently.[19,27]

Dermatologic manifestations are quite common in patients with ATLL and HAM/TSP and in asymptomatic HTLV-1 carriers.[29,30] The similarity of IDH to other dermatological conditions such as atopic dermatitis and seborrheic dermatitis and clinical speciousness may lead to the misdiagnosis and underreporting of IDH cases.[6,19] As dermatological examination is the only method currently available to differentiate IDH from other skin conditions, the skin clinical exam should be carefully done to improve the opportunity for IDH diagnosis.[6,20]

No evidence of immunodeficiency was observed when analyzing T-cell CD4 and CD8 counts. All three patients showed increased T-cell lymphocyte proliferation responses and in two cases, which proviral load was performed, the results showed high levels. This increased immune activation may have occurred as a result of HTLV-1 infection.[31] In fact, this finding is likely related to the neurological disease (HAM/TSP) associated with IDH in those adult patients.[32,33] It has been hypothesized that immune deregulation is responsible for the pathogenesis of HAM/TSP, IDH, and other HTLV-1-associated diseases.[17] In the case of IDH, production of some cytokines and beta-chemokines may be responsible for sustaining the characteristics of the intense cutaneous inflammatory reaction, possibly accounting for the intractable nature of this disease.[34]

Because of HAM/TSP, all three patients received intravenous corticosteroids; patients also received antibiotics to treat urinary infections that arose as a complication of HAM/TSP. Consequently, we observed improvement of IDH symptoms without the use of antibiotics usually used to treat IDH, such as oral trimethoprim–sulfamethoxazole.[27] Although only three of the 73 adult patients with HAM/TSP developed IDH during follow-up, this association occurred during advanced HAM/TSP disease in all three patients. Additionally, one HAM/TSP/IDH patient died during follow-up. Thus, IDH can be used as a clinical marker for disease progression, and its development is indicative of poor prognosis for patients with HAM/TSP.

Finally, it has been shown that IDH may progress to ATLL and HAM/TSP.[25,27,35] Thus, in our hypothesis, the inverse can also occur (i.e., development of HAM/TSP in adults may represent an increased risk for the development of other inflammatory HTLV-1-associated diseases). Because IDH and HAM/TSP are immune deregulation conditions and the skin is an important site for HTLV-1 infection, dermatologists should be aware of these diagnoses and be included in the multidisciplinary HTLV diagnostic group.

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