Report

Human T-cell lymphotropic virus type 1 infective dermatitis emerging in adulthood

Luciana Maragno, Clinical fellow, **Jorge Casseb,** Assistant professor, **Ligia Maria I. Fukumori,** Biology technician, **Mirian Nacagami Sotto,** Associate professor, **Alberto José da Silva Duarte,** Associate professor, **Cyro Festa-Neto,** Associate professor, **and José Antônio Sanches,** Associate professor

From the Department of Dermatology, "Hospital das Clínicas," University of São Paulo Medical School, São Paulo, Brazil

Correspondence
Luciana Maragno, Clinical fellow
Rua José Meza Mendonça, 132
CEP. 09750 – 390 – Jardim do Mar
São Bernardo do Campo – SP
Brazil
E-mail: lucianamaragno@terra.com.br

Abstract

Background Infective dermatitis (ID) is a rare dermatologic condition of childhood that has been linked to human T-cell lymphotropic virus type 1 (HTLV-1).

Objective To analyze the clinical and laboratory features associated with adult-onset ID linked to HTLV-1.

Methods From December 1995 to December 2007, four patients with ID were followed in the dermatology outpatient clinic of the "Hospital das Clínicas" of the University of São Paulo Medical School, São Paulo, Brazil. Epidemiologic data were collected and dermatologic examination was performed. Patients were submitted to histopathologic, hematologic, virologic, and immunologic investigations.

Results All patients had a diagnosis of ID according to previously established criteria, despite being adults. HTLV-1 infection was demonstrated by enzyme-linked immunosorbent assay, Western blotting assays, and polymerase chain reaction. The male to female ratio was 1 : 3 and the median age at diagnosis was 42 years. The cutaneous manifestations were erythematous, scaly, and crusted lesions in all patients, and ichthyosis in three of the four cases. Histopathologic study showed lymphocytic epidermotropism in two cases. The median proviral load was 281 copies/10,000 peripheral blood mononuclear cells. Immunodeficiency was not observed in any case. The therapies used were antimicrobials, corticosteroids, and phototherapy.

Conclusions Although many authors have considered ID to be a form of childhood dermatitis, we have described four cases that fulfilled the major criteria for ID, except for onset in adulthood.

Introduction

In 1980, human T-cell lymphotropic virus type 1 (HTLV-1) was the first retrovirus linked to human disease. It is an enveloped, double-stranded RNA, type C virus (family Retroviridae; genus *Deltaretrovirus*).[1] HTLV-1 can infect various cell types, including T cells, B cells, monocytes, and fibroblasts, by the receptor glucose transporter type 1 (GLUT1).[2] The major routes of transmission are mother-to-infant transmission (mainly through breastfeeding), sexual transmission (mainly from male to female), and parenteral transmission (blood transfusion or intravenous drug use).[3]

There are approximately 15–20 million HTLV-1 carriers in the world, with major endemic foci in Japan, the Caribbean Islands, Africa, and South America, particularly Brazil.[4,5] In Brazil, the seroprevalence has been estimated to be approximately 0.41%, ranging from 0.1% in the blood donor population in the state of Minas Gerais (south-eastern region) to 1.4% in the state of Bahia (north-eastern region).[6] Most (97%) HTLV-1-infected individuals develop no associated disease. The mechanisms involved in the pathogenesis of HTLV-1-associated disease remain unresolved.[7]

HTLV-1 has been associated with adult T-cell leukemia/lymphoma (ATLL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), HTLV-associated uveitis, and HTLV-1-associated infective dermatitis (ID).[8] Other diseases have been related to the virus in adulthood, such as lymphocytic T-cell alveolitis, Sjögren's syndrome, thyroiditis, Behçet's disease, arthropathy, and polymyositis.[9]

Dermatologic manifestations are quite common in patients with ATLL and HAM/TSP. Even in asymptomatic HTLV-1 carriers, skin lesions are also frequent. Nobre *et al.*[10] have classified the dermatologic alterations observed in patients with HTLV-1 and HTLV-1-associated diseases, caused by immunodeficiency and nonspecific lesions. The most common skin diseases are acquired ichthyosis,[11] xerosis, scabies, seborrheic dermatitis, vitiligo, and cutaneous mycosis.[10]

The condition of ID was first characterized in Jamaican children by Sweet (as cited by Maloney), in 1966, as an exudative and crusting dermatitis with frequent relapse after

treatment, and was later related to HTLV-1.[12] The frequency of ID is greater in females, with an onset generally after 18 months of age (rarely, it persists until adulthood).[3] This disease is considered to be a risk factor for the development of ATLL and HAM/TSP.[1,13]

The major diagnostic criteria, proposed by La Grenade *et al.*[14] in 1998, include the following: dermatitis of the scalp, axillae and groin, external ear and retroauricular areas, eyelid margins, paranasal skin, and/or neck; chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares; early childhood-onset or chronic relapsing dermatitis; and HTLV-1 antibody seropositivity. Among the minor or less specific criteria are positive cultures for *Staphylococcus aureus* and/or β-hemolytic streptococci from the skin or the anterior nares, generalized fine papular eruption, generalized lymphadenopathy with dermopathic lymphadenitis, anemia, elevated erythrocyte sedimentation rate, hyperimmunoglobulinemia, and elevated CD4 count, CD8 count, and CD4/CD8 ratio.

The diagnosis is based almost exclusively on the clinical aspects of the disease, and it is necessary to differentiate it from atopic dermatitis and seborrheic dermatitis. Histopathologic examination shows similar aspects to other types of chronic dermatitis.[15] Like other forms of dermatitis, histologically, ID may represent a benign simulator of mycosis fungoides.[13] The disease responds to antimicrobials and corticosteroids (topical and/or systemic), but relapses when antimicrobials are withdrawn.[16]

To our knowledge, there have been only two well-documented cases of adult-onset ID from Bahia, Brazil, in the world literature.[17] This report describes the clinical and laboratory features of four ID cases emerging in adulthood.

Materials and Methods

Patients

The study population consisted of four adults, who attended the dermatology outpatient clinic of the University of São Paulo between December 1995 and December 2007. A clinical history and dermatologic examination were performed at each clinic visit. All patients were evaluated for neurologic and ocular involvement. The diagnosis of ID was made according to previously established criteria. Patients underwent laboratory studies, including routine examinations, punch skin biopsies, skin cultures, stool microscopy, flow cytometry, and lymphocyte proliferation on stimulation with various different antigens and mitogens.

Serologic diagnosis

Antibodies to HTLV-1 were detected by diagnostic enzyme-linked immunosorbent assay (ELISA), and were confirmed by Western blot and polymerase chain reaction (PCR), which are capable of discriminating between HTLV-1 and HTLV-2. Serologic assays for human immunodeficiency virus (HIV) were also performed using ELISA.

Histopathologic and immunohistochemical studies

Punch skin biopsies were taken from the involved areas (mainly the scalp and other seborrheic areas) of all patients. The biopsies were fixed in 10% buffered formalin, the blocks were embedded in paraffin, and histologic sections were stained with hematoxylin and eosin. Immunohistochemical investigation of lymphoid cells was performed in paraffin-embedded sections using anti-CD4 (clone OPD4/CD45RO, Dako, Copenhagen, Denmark) and anti-CD8 (clone C8/144B, Dako).

Flow cytometry

Antibodies against CD2, CD3, CD4, CD5, CD7, CD8, T-cell receptor (TCR)αβ, TCRγδ (T lymphocyte), CD25 (interleukin-2 receptor), CLA+ (cutaneous lymphocyte antigen), CD19 (B lymphocyte), and CD3–/16+/56+ [natural killer (NK) cell] were used to measure lymphocyte populations and subsets (FACSCalibur, BD Biosciences, San Jose, CA, USA), and the data were analyzed using CellQuest software (BD Biosciences, San Jose, CA, USA).

Proviral load

Quantitative proviral DNA levels were detected by a real-time automated PCR method using TaqMan probes for the *pol* gene. The *albumin* gene was the internal genomic control and MT2 cells were used as positive control. The results are reported as copies/10,000 peripheral blood mononuclear cells (PBMCs), and the detection limit was 10 copies.

Lymphocyte proliferation

The PBMCs were cultivated in flat-bottomed plates (Costar, Cambridge, MA, USA) at 37 °C and 5% CO_2 in the presence of mitogens, such as phytohemagglutinin (PHA) (Gibco BRL, New York, NY, USA) and "Pokeweed" (PWM) (Sigma, St. Louis, MO, USA), and antigens, such as OKT3 (a murine monoclonal IgG2a antibody that reacts with the T-cell receptor-CD3 complex on the surface of circulating human T-cells) and *Candida albicans* extract (CMA) (Sanofi-Pasteur, Lyon, France), for 6, 24, and 72 h. Cell proliferation was quantified by determining the uptake of [^{3}H]thymidine (Radiochemical Centre, Amersham, UK), added before automatic harvesting of the cells (Combicell Harvester, Skatron, Lier, Norway), and liquid scintillation counting (Betaplate 1205, Wallac Oi, Turku, Finland).

Results

During the period December 1995 to December 2007, 20 HTLV-1-seropositive patients with dermatologic lesions were evaluated. The dermatologic alterations observed included erythroderma (6/20), ID/seborrheic dermatitis (6/20), papules, plaques, and/or nodules (7/20), and disseminated acquired ichthyosis (1/20). Histopathologic assessment revealed epidermotropism of lymphocytes, suggestive of cutaneous lymphoma, in 14 cases, and five samples presented nonspecific findings; one patient did not undergo histopathologic study.

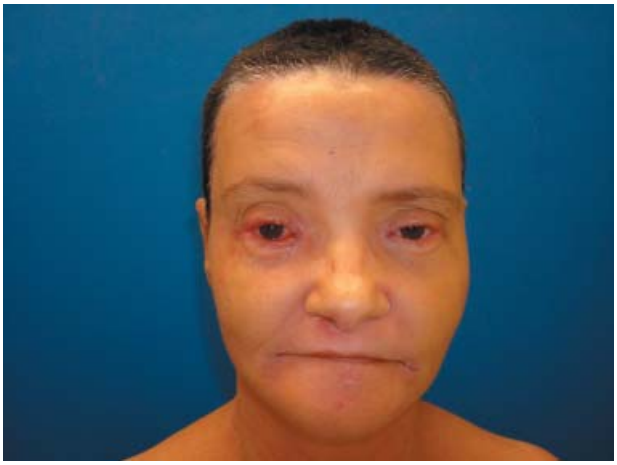

Figure 1 Case 3: erythematous, exudative, and crusted lesions on the scalp, face, and neck

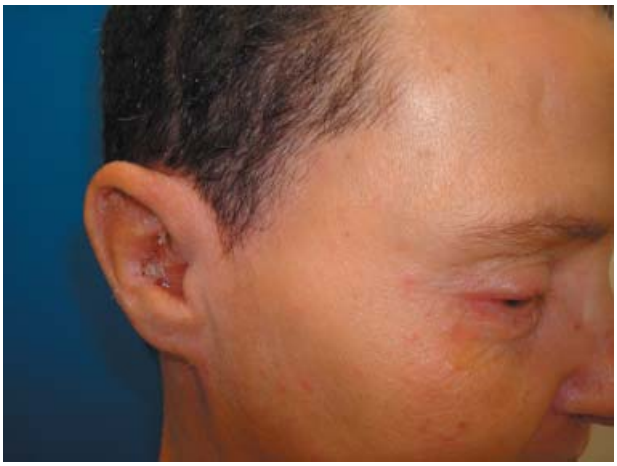

Figure 2 Case 3: severe involvement of the scalp and external ear, with exudative and crusted lesions

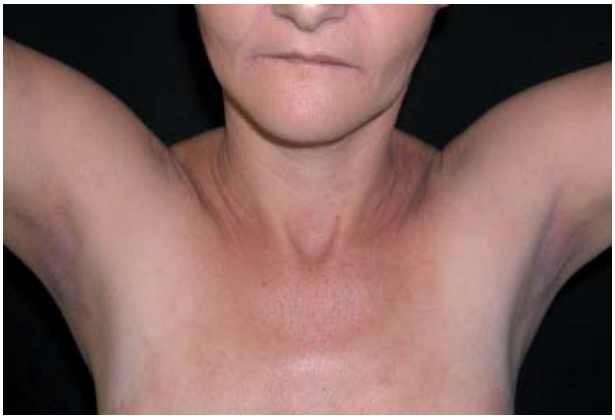

Figure 3 Case 3: erythematous and scaly lesions on the face, neck, trunk, and armpits

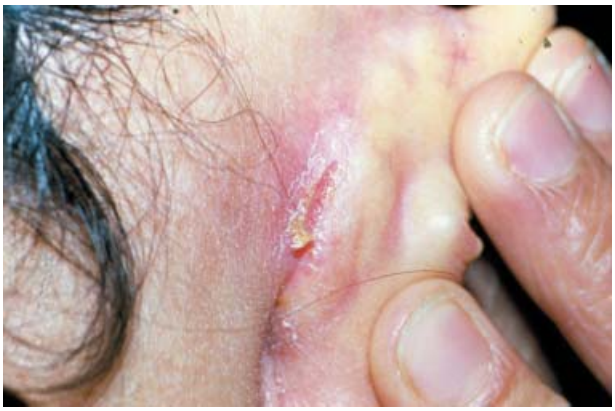

Figure 4 Case 2: retroauricular fissures

Adult-onset ID was diagnosed in four individuals: three women and one man. The median age at diagnosis was 42 years, ranging from 34 to 57 years. Two patients were from south-eastern Brazil (nonendemic area), one was from the north-east, and one was from the north (both endemic areas). According to the patient information, the time from dermatologic manifestation to the diagnosis of ID ranged from 12 to 24 months (median, 19.2 months). The patients were followed up for a median of 4.9 years (range, 2.1–8.3 years) and, until the last attendance, none showed the development of hematologic or neurologic disorders (Table 1).

Dermatologic examination revealed erythematous, scaly, and crusted lesions on the scalp, neck, ears, and other parts of the body in four patients (Figs 1–4) Ichthyosis was observed in three of the four patients. Other skin manifestations included poikiloderma (1/4) and folliculitis (1/4). Two patients presented with nasal discharge with crusting on the nostrils. Neurologic examination was performed in all cases, and only one showed neurologic alterations (generalized hyperreflexia).

Histopathologic study revealed lymphocytic epidermotropism in two of the four samples: psoriasiform dermatitis in one case and spongiosis with perivascular dermatitis in the other (Table 2; Figs 5–8). The inflammatory infiltrate consisted of CD4+ and CD8+ cells in a similar ratio, in both the epidermis and dermis in all cases (Figs 9 and 10). Skin cultures for bacterial pathogens were performed for three patients and were positive for *S. aureus* in two; in one patient, a simultaneous infection with *S. aureus* and *Streptococcus β-hemolyticus* was observed. Stool examination performed in three cases was negative for parasites, ova, and cysts (Table 2).

In the hematologic analysis, the white blood cell count was low in one of the four cases (median, 4800 cells; range, 3900–10,020), associated with lymphopenia. Lymphocytosis was observed in one case (median, 2204 cells; range, 718–3900).

Table 1 Clinical data of the patients

Case	Sex/color	Age (years)	Duration of ID (months)	Dermatologic manifestation	Neurologic manifestation
1	Female/Mulatto	57	24	Erythematous, scaly, and crusted lesions and ichthyosis	None
2	Female/white	37	17	Erythematous, scaly, and crusted lesions, ichthyosis, poikiloderma, and folliculitis	Generalized hyperreflexia
3	Female/white	43	12	Erythematous, scaly, and crusted lesions and ichthyosis	None
4	Male/white	34	24	Erythematous, scaly, and crusted lesions	None

ID, infective dermatitis.

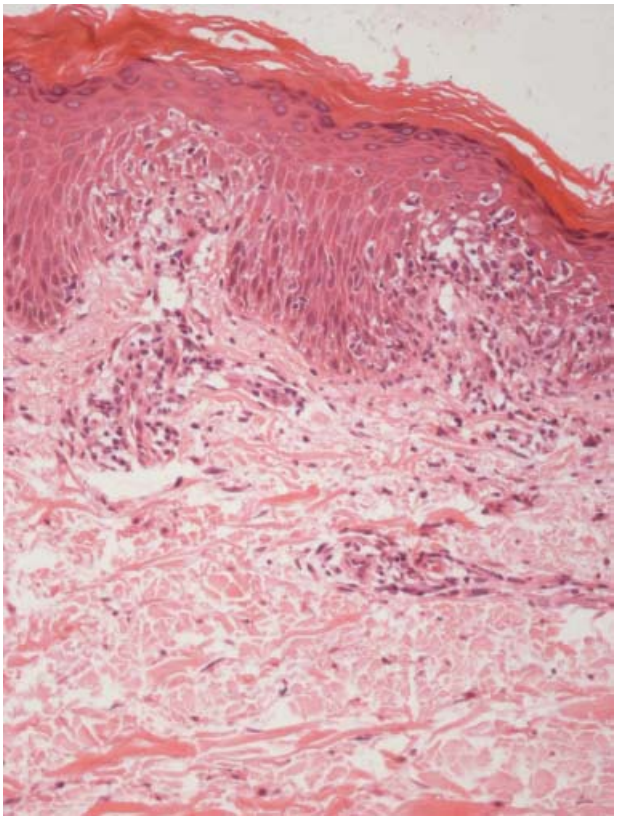

Figure 5 Hyperkeratosis and acanthosis with elongation of the rete ridges and exocytosis of lymphoid cells; perivascular mononuclear cell infiltration in the dermis with a predominance of lymphocytes (hematoxylin and eosin; original magnification, ×100)

A small number of lymphocytes (less than 5%) with some nuclear irregularities (pleomorphic lymphocytes) were detected in three of the four patients. Two patients presented with relative and absolute eosinophilia (median, 465 cells; range, 202–684) (Table 3). Biochemical laboratory examinations yielded normal findings.

In all cases, antibodies to HTLV-1 were detected by diagnostic ELISA, and were confirmed by Western blotting and PCR. The proviral DNA load in these patients was 281 copies/10,000 PBMCs, with a range of 10–400 copies (Table 2). Serologic testing for HIV was negative for all patients at the start of the investigation; however, one case presented with HIV seroconversion during follow-up (Case 3).

On analysis of the lymphocyte subsets by flow cytometry, all patients had normal counts of CD3+ (median, 74.75%; range, 63–82%), NK (median, 11.25%; range, 4–19%), TCRγδ (median, 3.5%; range, 2–5%), B lymphocytes (median, 12.25%; range, 7–18%), and CD4+ (median, 43.5%; range, 30–54%), and a normal CD4+/CD8+ ratio (median, 1.9; range, 0.6–3.1). Only one patient presented an increase in the CD8+ count (49%) (Table 4). No loss of mature T-cell markers or phenotypic abnormalities were observed. No increase in T lymphocytes expressing CLA was observed in three cases. In relation to the expression of CD25+ in T lymphocytes, two cases demonstrated increased counts.

Of the patients submitted to the lymphocyte proliferative response on stimulation by mitogens (PHA and PWM) and antigens (OKT3 and CMA), all showed a normal response.

With regard to the therapeutic modalities, topical corticosteroids were used in all cases, with or without systemic antimicrobials, and phototherapy was used by three patients [psoralen plus ultraviolet A (PUVA) and/or narrow-band UVB].

Discussion

ID is a chronic and recurrent dermatitis occurring in vertically infected carriers during childhood and adolescence. The cases reported in this paper fulfilled the major criteria for the diagnosis of ID, established by La Grenade *et al.*,[14] although two patients did not present with chronic nasal discharge and/or

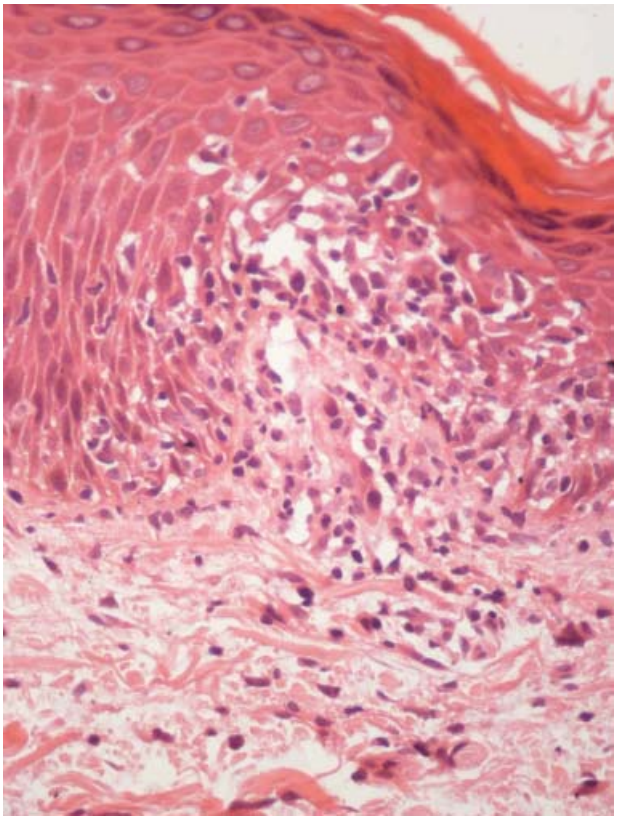

Figure 6 Prominent exocytosis of lymphoid cells (hematoxylin and eosin; original magnification, ×200)

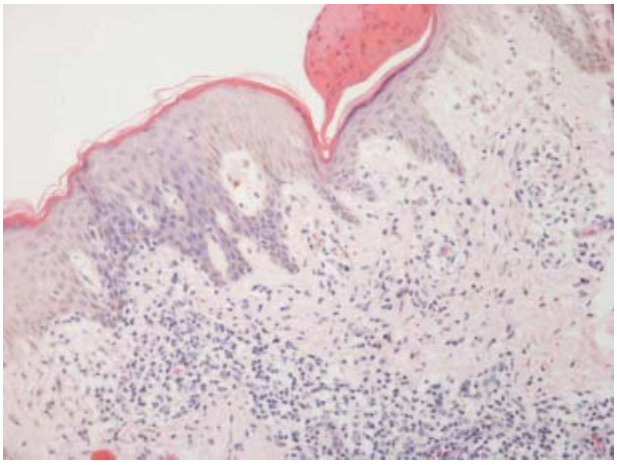

Figure 7 Epidermis with irregular acanthosis and scale-crusts; moderate perivascular lymphocytic infiltrate with halos around the lymphocytes invading the basal layer of the epidermis (hematoxylin and eosin; original magnification, ×40)

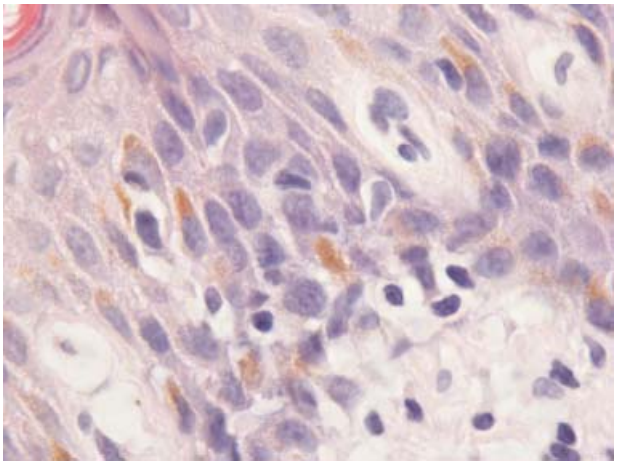

Figure 8 Halos around the lymphocytes with infolded nuclear contours (hematoxylin and eosin; original magnification, ×400)

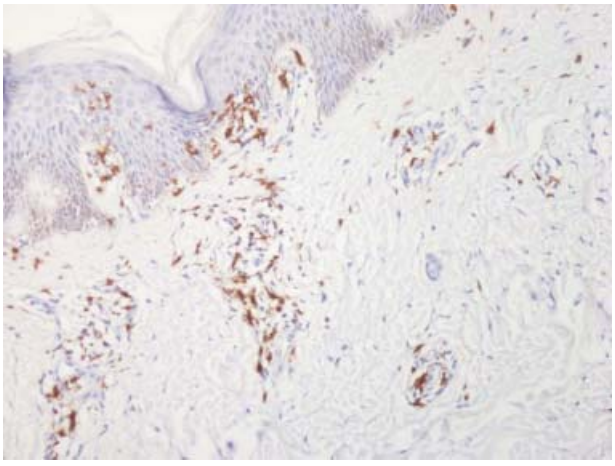

Figure 9 CD4+ lymphocytes in the epidermis and dermis (×200)

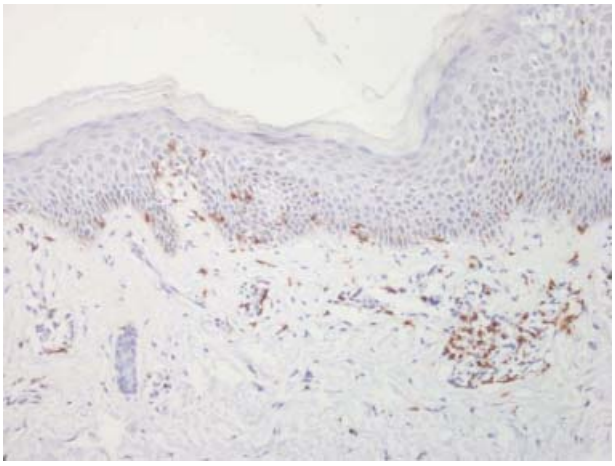

Figure 10 CD8+ lymphocytes in the epidermis and dermis (×200)

Table 2 Laboratory data of the patients

Case	Histopathology	Skin culture	Proviral load (copies/10,000 PBMCs)	Treatment
1	Lymphocytic epidermotropism	Positive for *Staphylococcus aureus* and *Streptococcus β-hemolyticus*	400	Antimicrobials (systemic), corticosteroids (topical)
2	Lymphocytic epidermotropism	Not done	440	Corticosteroids (topical)
3	Psoriasiform dermatitis	Positive for *S. aureus*	< 10	Antimicrobials (systemic), corticosteroids (topical), and phototherapy (PUVA, UVB)
4	Spongiosis with perivascular dermatitis	Positive for *S. aureus*	323	Antimicrobials (systemic), corticosteroids (topical), and phototherapy (UVB)

PBMC, peripheral blood mononuclear cell; PUVA, psoralen plus ultraviolet A.

Table 3 Hematologic data of the patients

Case	Leukocytes (/mm^3)	Lymphocytes (/mm^3)	Eosinophils (/mm^3)
Reference value	4000–11,000	900–3400	50–500
1	3900	718	351
2	5700	1700	684
3	8580	2500	626
4	10,020	3900	202

Table 4 Flow cytometry data (%) of the patients

Case	TCRαβ	CD2	CD3	CD5	CD7	CD4	CD8	NK	TCRγδ	CLA+	CD19	CD25	CD4 : CD8
Reference value	51–78	55–82	60–86	57–81	42–76	31–60	11–38	1–22.5	1–15	0–7	3,5–19	3–25	0.4–3.6
1	54	61	63	63	43	40	19	19	4	8	13	18	2.1
2	75	82	82	81	65	50	29	4	2	1	10	30	1.7
3	77	82	81	77	74	30	49	11	5	3	7	12	0.6
4	70	72	73	72	64	54	17	11	3	1	18	37	3.1

CLA, cutaneous lymphocyte antigen; NK, natural killer; TCR, T-cell receptor.

crusting in the nostrils and the disease developed in adulthood. The diagnosis of ID is mainly clinical, and it is necessary to differentiate it from atopic dermatitis and seborrheic dermatitis.[18] No patient in this study had a personal history of atopia, pruritus was not an important complaint in any of the cases, and the lesions presented were exudative and infected. All lesions showed a good response to antimicrobials, which is not characteristic of seborrheic dermatitis.

Only two cases of adult-onset ID have been reported in the world literature. These cases were reported by Bittencourt *et al.*[17] in Bahia, an endemic area in Brazil. The same group also reported a study of 23 children with ID,[18] revealing that the disease is more frequent in childhood. Although our outpatient clinic is a referral center for pediatric dermatology, no childhood ID cases have been seen, but four cases have been found in adults. This may indicate that socioeconomic and environmental factors play an important role in the development of ID, and could determine the latency period. It is also possible that some cases of ID may be misdiagnosed as atopic or seborrheic dermatitis.

All patients included in this report were submitted to dermatologic, neurologic, and ophthalmologic examination. Only one (Case 2) showed abnormality in the neurologic examination (generalized hyperreflexia), not yet diagnostic for HAM/TSP. HAM/TSP is a chronic myelopathy associated with HTLV-1 infection, more common in female patients in the fourth or fifth decade of life, and is characterized by slowly progressive spastic paraparesis, usually associated with bladder disturbance and sensory involvement.[4,7,19] Persistent hyperreflexia of the lower limbs is a clinical feature of HAM/TSP, in addition to spasticity, difficult walking, weakness of the lower limbs, and bladder dysfunction.[20] There is an established association between ID and HAM/TSP,[4] determined by genetic factors, immunologic response, and proviral

load.[4,15,21,22] In our cases, despite a median follow-up of 4.9 years, no patient has yet presented with a neurologic disorder associated with HTLV-1 infection.

HIV/HTLV-1 coinfection is frequent, mainly in metropolitan areas where intravenous drug use is a common mode of viral transmission;[20,23,24] however, the long-term effects of this association are unknown.[8] Serologic assays for HIV were performed in all cases and, initially, all were seronegative; however, Case 3 presented with HIV seroconversion during follow-up. This patient has developed a significant worsening of her ID manifestations, but has not yet progressed to acquired immunodeficiency syndrome (AIDS).

The histopathologic analysis of our patients showed epidermotropism of lymphocytes in two of four cases. This finding has been reported previously by Bittencourt *et al.*[13,17] during the investigation of ID cases in children and adults. Milagres *et al.*[11] also reported this histopathologic feature in cases of acquired ichthyosis associated with HAM/TSP. The presence of abnormal lymphocytes in asymptomatic HTLV-1 carriers may be associated with a high proviral load, and can be predictive of the greatest risk of developing ATLL and HAM/TSP.[1]

Some authors have considered ID to be part of a prodromal phase associated with ATLL.[15,25] ATLL is a neoplastic disease of CD4+ lymphocytes, etiologically linked to HTLV-1. Three diagnostic criteria for ATLL have been defined: the presence of morphologically proven lymphoid malignancy with T-cell surface antigens (typically CD4+, CD25+); the presence of antibodies to HTLV-1 in the sera; and the demonstration of monoclonal integration of HTLV-1 provirus in tumor cells by Southern blotting.[26,27] It is fundamental to differentiate ID from epidermotropic cutaneous T-cell lymphoma (CTCL), because ATLL may sometimes present with this histopathologic pattern.[3,12,17,25] Our patients showed the clinical features, treatment response, and evolution suggestive of ID, rather than cutaneous lymphoma, and immunohistochemistry showed a similar amount of CD4+ and CD8+ T cells in both the dermis and epidermis in all cases.

Many studies on the HTLV-1 proviral burden have been reported in the world literature, but the proviral load in ID has not been investigated. Thus, the HTLV-1 proviral load during the asymptomatic phase of infection is generally lower than that in ATL and HAM/TSP.[28] Montanheiro *et al.*[22] reported median proviral loads in asymptomatic HTLV-1-infected carriers of 271 and 679 copies/10,000 PBMCs in HAM/TSP cases. Our patients had a median proviral DNA load of 281 copies/10,000 PBMCs, which is similar to the asymptomatic phase of the disease. We need to examine whether this low proviral load, seen in our patients, could be associated with the development of ID in adulthood. More studies on HTLV-1 infection, proviral load, and ID should be performed to try to answer this and other related questions.

With regard to the analysis of lymphocyte subsets, this report showed an increase in the CD25+ T-cell count in two cases. This finding, associated with the fact that two patients presented with eosinophilia, suggests a T-helper-2 (Th2) cytokine profile. An increase in the CD8+ T-cell count was observed in only one case. Previous reports have suggested that increased circulating CD4+ and CD8+ cells and an increased CD4/CD8 ratio are features of ID.[14,16] It has been shown previously that the efficiency of an individual's cytotoxic T-cell response against HTLV-1 is important in an individual's proviral load.[29–31]

HTLV-1 is a complex retrovirus that resides in immune cells of central importance for immunoregulation, and functionally alters them.[32] Patients with ATLL are profoundly immunocompromised and are prone to other malignancies and opportunistic infections caused by various pathogens (such as *Pneumocystis jiroveci*, cytomegalovirus, *Strongyloides*, and *Mycobacterium*).[26] Mild immunodeficiency is also seen in asymptomatic carriers.[33] Several theories have been proposed to explain this immune dysfunction. One involves a decrease in the number of naive T lymphocytes;[33] however, the main host cells infected by HTLV-1 are CD4+/CD25+ T cells, which have suppressive immunoregulatory functions; thus, ATLL cells can be considered to downregulate the immune response.[19] In three of the four cases submitted to lymphocyte proliferative response assay on stimulation with different antigens (OKT3 and CMA) and mitogens (PHA and PWM), no evidence of immunodeficiency was observed. This is the first study of the immune response in ID using this methodology.

Our report suggests that the early identification of ID cases through serologic screening for HTLV-1 in adult patients with chronic, relapsing, and severe dermatitis in HTLV-1-endemic regions is important to prevent further dissemination (counseling infected individuals on sexual practices, and reducing the duration of or, if possible, stopping breastfeeding by HTLV-1-infected mothers), to provide effective management of ID and commonly associated conditions, and to permit a careful follow-up for the early detection of complications, such as HAM/TSP or ATLL.[34]

References

1 Manns A, Hisada M, La Grenade L. Human T-lymphotropic virus type I infection. *Lancet* 1999; **353**: 1951–1958.
2 Sibon D, Gabet AS, Zandecki M, *et al.* HTLV-1 propels untransformed CD4+ lymphocytes into the cell cycle while protecting CD8+ cells from death. *J Clin Invest* 2006; **116**: 974–983.
3 Bittencourt AL, Primo J, Oliveira MFP. Manifestation of the human T-cell lymphotropic virus type I infection in childhood and adolescence. *J Pediatr (Rio J)* 2006; **82**: 411–420.
4 Primo JRL, Brites C, Oliveira MFSP, *et al.* Infective dermatitis and human T cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis

in childhood and adolescence. *Clin Infect Dis* 2005; **41**: 535–541.
5 Proietti FA, Carneiro-Proietti ABF, Catalan-Soares BC, *et al*. Global epidemiology of HTLV-I infection and associated diseases. *Oncogene* 2005; **24**: 6058–6068.
6 Gonçalves DU, Guedes ACM, Proietti ABFC, *et al*. Dermatologic lesions in asymptomatic blood donors seropositive for human T-cell lymphotropic virus type 1. *Am J Trop Med Hyg* 2003; **68**: 562–565.
7 Furukawa Y, Kubota R, Eiraku N, *et al*. Human T-cell lymphotropic virus type I (HTLV-I)-related clinical and laboratory findings for HTLV-I-infected blood donors. *J Acquir Immune Defic Syndr* 2003; **32**: 328–334.
8 Farre L, Oliveira MFP, Primo J, *et al*. Early sequential development of infective dermatitis, human T cell lymphotropic virus 1-associated myelopathy, and adult T cell leukemia/lymphoma. *Clin Infect Dis* 2008; **46**: 440–442.
9 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**: e136–e142.
10 Nobre V, Guedes ACM, Proietti FA, *et al*. Dermatologic lesions in patients infected with the human T-cell lymphotropic virus type 1 (HTLV-1). *Rev Soc Bras Med Trop* 2005; **38**: 43–52.
11 Milagres SP, Sanches JA Jr, Milagres ACP, *et al*. Histopathological and immunohistochemical assessment of acquired ichthyosis in patients with human T-cell lymphotropic virus type I-associated myelopathy. *Br J Dermatol* 2003; **149**: 776–781.
12 Maloney EM, Hisada M, Palmer P, *et al*. Human T cell lymphotropic virus type I-associated infective dermatitis in Jamaica: a case report of clinical and biologic correlates. *Pediatr Infect Dis J* 2000; **19**: 560–565.
13 Bittencourt AL, Oliveira MF, Brites C, *et al*. Histopathological and immunohistochemical studies of infective dermatitis associated with HTLV-I. *Eur J Dermatol* 2005; **15**: 26–30.
14 La Grenade L, Manns A, Fletcher V, *et al*. Clinical, pathologic, and immunologic features of human T-lymphotropic virus type I-associated infective dermatitis in children. *Arch Dermatol* 1998; **134**: 439–444.
15 Oliveira MF, Bittencourt AL, Brites C, *et al*. HTLV-I associated myelopathy/tropical spastic paraparesis in a 7-year-old boy associated with infective dermatitis. *J Neurol Sci* 2004; **222**: 35–38.
16 Pérez CL, Villarroel BJ, Reyes JA, *et al*. Eritrodermia exfoliativa y dermatitis infecciosa em um lactante infectado por El vírus linfotrópico humano-I (HTLV-I). *Rev Chil Infectol* 2007; **24**: 142–148.
17 Bittencourt AL, Oliveira MF, Ferraz N, *et al*. Adult-onset infective dermatitis associated with HTLV-I. Clinical and immunopathological aspects of two cases. *Eur J Dermatol* 2006; **16**: 62–66.
18 Oliveira MFSP, Brites C, Ferraz N, *et al*. Infective dermatitis associated with the human T cell lymphotropic virus type I in Salvador, Bahia, Brazil. *Clin Infect Dis* 2005; **40**: e90–e96.
19 Bangham CRM. HTLV-1 infections. *J Clin Pathol* 2000; **53**: 581–586.
20 Beilke MA, Traina-Dorge VL, Sirois M, *et al*. Relationship between human T lymphotropic virus (HTLV) type 1/2 viral burden and clinical and treatment parameters among patients with HIV type 1 and HTLV-1/2 coinfection. *Clin Infect Dis* 2007; **44**: 1229–1234.
21 Manns A, Miley WJ, Wilks RJ, *et al*. Quantitative proviral DNA and antibody levels in the natural history of HTLV-I infection. *J Infect Dis* 1999; **180**: 1487–1493.
22 Montanheiro PA, Oliveira ACP, Posada-Vergara MP, *et al*. Human T-cell lymphotropic virus type I (HTLV-I) proviral DNA viral load among asymptomatic patients and patients with HTLV-I associated myelopathy/tropical spastic paraparesis. *Braz J Med Biol Res* 2005; **38**: 1643–1647.
23 Bangham CRM, Hall SE, Jeffery KJM, *et al*. Genetic control and dynamics of the cellular immune response to the human T-cell leukaemia virus, HTLV-I. *Philos Trans R Soc London B* 1999; **354**: 691–700.
24 Beilke MA, Theall KP, O'Brien M, *et al*. Clinical outcomes and disease progression among patients coinfected with HIV and human T lymphotropic virus types 1 and 2. *Clin Infect Dis* 2004; **39**: 256–263.
25 Gonçalves DU, Guedes AC, Carneiro-Proietti ABF, *et al*. HTLV-I associated infective dermatitis may be an indolent HTLV-I associated lymphoma. *Braz J Infect Dis* 2000; **4**: 100–102.
26 Yasunaga JI, Matsuoka M. Human T-cell leukemia virus type I induces adult T-cell leukemia: from clinical aspects to molecular mechanisms. *Cancer Control* 2007; **14**: 133–140.
27 Matutes E. Adult T-cell leukaemia/lymphoma. *J Clin Pathol* 2007; **60**: 1373–1377.
28 Gabet AS, Kazanji M, Couppie P, *et al*. Adult T-cell leukaemia/lymphoma-like human T-cell leukaemia virus-1 replication in infective dermatitis. *Br J Haematol* 2003; **123**: 406–412.
29 Asquith B, Bangham CRM. The role of cytotoxic T lymphocytes in human T-cell lymphotropic virus type 1 infection. *J Theor Biol* 2000; **207**: 65–79.
30 Bangham CRM, Osame M. Cellular immune response to HTLV-1. *Oncogene* 2005; **24**: 6035–6046.
31 Bangham CRM. The immune control and cell-to-cell spread of human T-lymphotropic virus type 1. *J Gen Virol* 2003; **84**: 3177–3189.
32 Hollsberg P. Mechanisms of T-cell activation by human T-cell lymphotropic virus type I. *Microbiol Mol Biol Rev* 1999; **63**: 308–333.
33 Yasunaga JI, Sakai T, Nosaka K, *et al*. Impaired production of naive T lymphocytes in human T-cell leukemia virus type I-infected individuals: its implications in the immunodeficient state. *Blood* 2001; **97**: 3177–3183.
34 Mahé A, Meertens L, Ly F, *et al*. Human T-cell leukaemia/lymphoma virus type 1-associated infective dermatitis in Africa: a report of five cases from Senegal. *Br J Dermatol* 2004; **150**: 958–965.

