Dermatological Findings of Human T Lymphotropic Virus Type 1 (HTLV-I)–Associated Myelopathy/ Tropical Spastic Paraparesis

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Dermatological findings for patients with human T lymphotropic virus type 1(HTLV-I)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) were investigated and were compared with dermatological findings for a control group. Only xerosis, cutaneous candidiasis, and palmar erythema were significantly associated with HAM/TSP. Histopathological patterns of cutaneous lymphoma were seen in 25% of 32 patients who underwent biopsy, and, thus, the cutaneous alterations in HAM/TSP can be classified into nonspecific lesions, infectious lesions, immune-inflammatory–mediated lesions, and premalignant or malignant lesions.

Human T lymphotropic virus type 1 (HTLV-I) was the first retrovirus found in humans. It was initially isolated from lymphocytes of a black man who had a cutaneous lymphoma [1]. Although HTLV-I infection is classically associated with the development of 2 diseases (HTLV-I–associated myelopathy/ tropical spastic paraparesis [HAM/TSP] and adult T cell leukemia/lymphoma [ATLL]), >95% of infected individuals remain asymptomatic [2, 3]. A genetic predisposition may be related to the pathogenesis of these diseases [4, 5].

ATLL is characterized by infiltration of the lymph nodes, spleen, and skin by malignant CD4 T cells [6]. There is a remarkable and frequent cutaneous involvement associated with ATLL, which can be highly variable among patients [7–9].

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Table 1. Dermatological findings for patients with human T lymphotropic virus type 1 (HTLV-I)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) and for HTLV-I–negative control subjects.

Dermatological finding	No. (%) of patients with HAM/TSP (n = 60)	No. (%) of control subjects (n = 38)	P value
Xerosis	49 (81.6)	14 (36.8)	<.0001
Dermatophytosis	21 (35.0)	11 (29.0)	NS
Seborrheic dermatitis	20 (33.3)	13 (34.2)	NS
Candidiasis	9 (15.0)	1 (2.6)	.045
Palmar erythema	9 (15.0)	0 (0)	.009
Chronic eczema	8 (13.3)	4 (10.5)	NS
Drug reaction	4 (6.7)	0 (0)	NS
Trophic ulcer	4 (6.7)	0 (0)	NS
Scabies	3 (5.0)	0 (0)	NS
Photosensitivity	3 (5.0)	0 (0)	NS
Edema	2 (3.3)	0 (0)	NS
Warts	2 (3.3)	2 (5.3)	NS
Contact dermatitis	1 (1.7)	0 (0)	NS
Erythema nodosum	1 (1.7)	0 (0)	NS
Erythroderma	1 (1.7)	0 (0)	NS
Folliculitis decalvans	1 (1.7)	0 (0)	NS
Pyogenic granuloma	1 (1.7)	0 (0)	NS
Livedo reticularis	1 (1.7)	0 (0)	NS
Madarosis	1 (1.7)	0 (0)	NS
Melasma	1 (1.7)	2 (5.3)	NS
Molluscum contagiosum	1 (1.7)	0 (0)	NS
Pityriasis versicolor	1 (1.7)	5 (13.2)	.003
Vitiligo	1 (1.7)	0 (0)	NS
Hypertrichosis	0 (0)	1 (2.6)	NS
Neurofibromatosis	0 (0)	1 (2.6)	NS
Insect bite reaction	0 (0)	1 (2.6)	NS
Normal findings of DE	9 (15)	5 (13.2)	NS

NOTE. Each patient could present with >1 finding simultaneously. DE, dermatological examination; NS, nonsignificant (P > .05).

Nonspecific cutaneous findings may precede hematological signs of disease for many years [8], and isolated infiltration of the skin may be the first sign of ATLL [9]. Cutaneous lesions may appear as nonspecific erythematous patches, such as papular lesions, nodular tumors, and erythroderma [10]. Also, some investigators have reported skin lesions very similar to those found in association with Sézary syndrome [11, 12].

Other dermatological findings associated with HTLV-I infection include infective dermatitis [13, 14] (an inflammation of the skin associated with *Staphylococcus aureus* infection in children from Jamaica [15]) and crusted scabies (which has

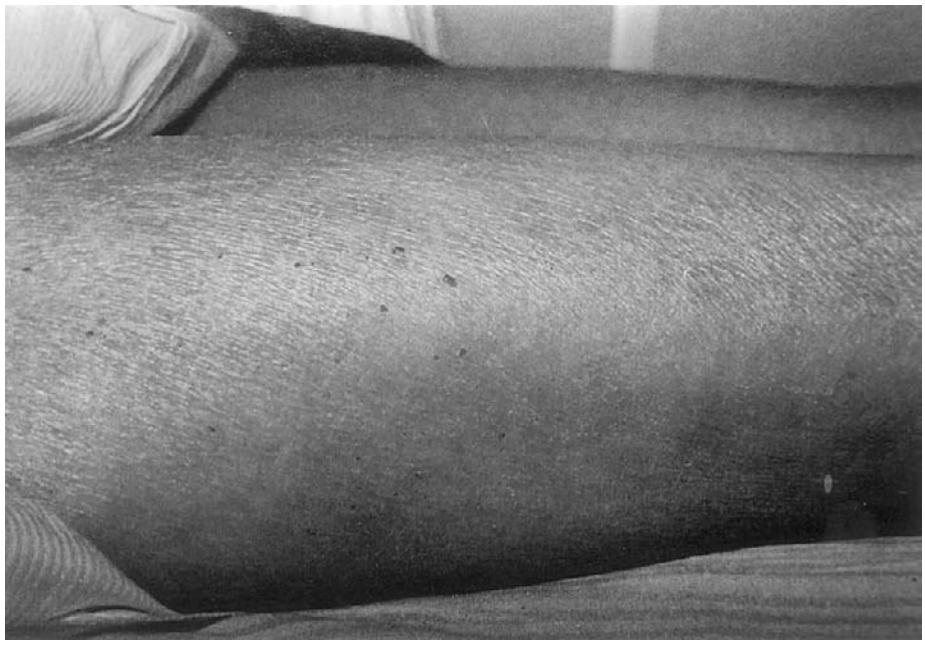

Figure 1. Xerosis and cutaneous atrophy of the thighs

been reported as a sign of subclinical HTLV-I infection [16], mainly among Australian Aborigines [17, 18]). Psoriasis, erythroderma, seborrheic dermatitis, and ichthyosiform eruptions have been reported among HTLV-I–infected patients [19].

HAM/TSP is an immune-mediated, chronic inflammatory neurological disease characterized by a slowly progressive spastic paraparesis, sphincter disturbances, and limited sensory signs [20]. In some areas of the world, such as Brazil, HAM/TSP is the most common cause of chronic progressive spastic paraparesis in adults [21]. In contrast with ATLL, there are only a few studies dealing with dermatological manifestations of HAM/TSP; most of these studies are single case reports or involve a small series of patients [22–27].

In the present study, we aim to demonstrate whether there is cutaneous involvement in patients with HAM/TSP. We also try to verify whether malignant histopathological patterns, sug-

Figure 2. Seborrheic dermatitis of the frontal region

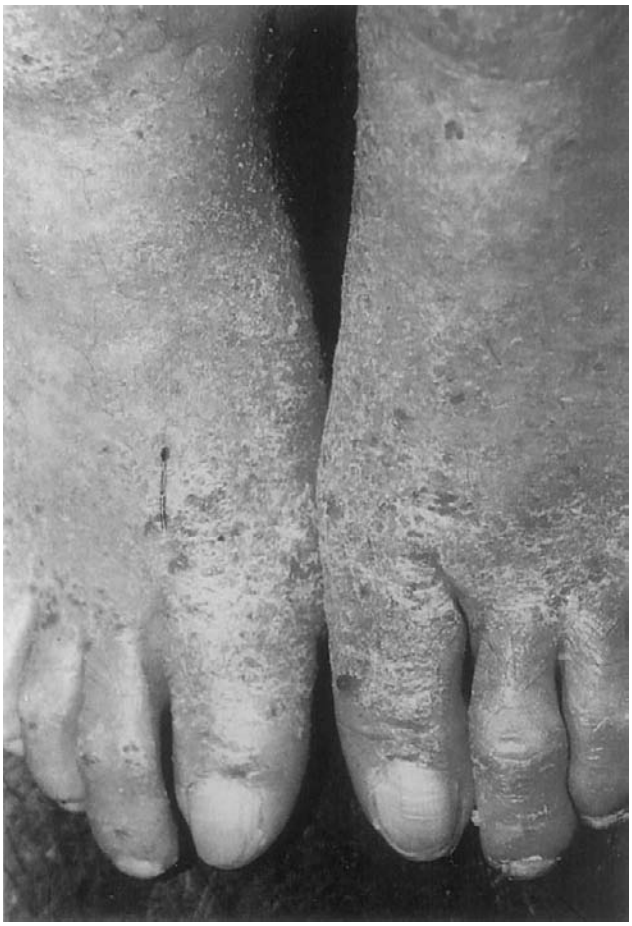

Figure 3. Crusted scabies of the feet

gestive of cutaneous T cell lymphoma, could be found in patients with HAM/TSP, even in the absence of clinical criteria for ATLL.

Patients and methods. The Reference Center for HTLV Infection at the Evandro Chagas Clinical Research Institute–Oswaldo Cruz Foundation (Rio de Janeiro, Brazil) followed a cohort of ~300 patients with HAM/TSP. All of them fulfilled internationally accepted criteria for the disease [23]. From July 1993 through July 1996, a total of 60 of these patients were randomly enrolled in this study. Patients who were coinfected (with HTLV-I/HIV or with HTLV-I/human T lymphotropic virus type 2) were excluded a priori. All patients were interviewed and examined by a senior dermatologist (M.E.R.L.). Special attention was given to risk factors for HTLV-I infection, evolution of the neurological disease, and dermatological abnormalities and their possible association with the myelopathy.

Patients with clinical evidence of dermatological involvement were randomly selected to undergo biopsy. Appropriate written and oral informed consent was obtained, and guidelines for human experimentation were followed in the conduct of the clinical research. After informed consent was obtained, 32 of the patients underwent punch skin biopsy. Thirty-eight age-matched HTLV-I–negative blood donors from the Blood Center of the University Hospital of the Federal Fluminense University, a major teaching hospital in Rio de Janeiro, Brazil, were considered to be the control group and were examined by the same dermatologist (M.E.R.L) who examined the patient group. For comparison of groups, χ^2 and Fisher exact tests were used, and a P value of $\leq .05$ was considered to be statistically significant.

Results. Most patients with HAM/TSP (51 [85%] of 60) had some dermatological abnormality (table 1). These patients clearly correlated their dermatological complaints with the beginning of the neurological disease. With respect to sex and skin color, 31 patients (51.7%) were female, 32 (53.3%) were white, 21 (35%) were mulattos, and 7 (11.7%) were black. The age distribution showed that 2 patients (3.4%) were <20 years of age, 6 (10%) were 21–40 years of age, 41 (68.3%) were 41–60 years of age, and 11 (18.3%) were >60 years of age. For 27 patients (45%), risk factors for infection were determined, with blood transfusion and sexual promiscuity observed equally often (11 patients [18.3%]), followed by injection drug use (6 patients [10%]) and then by a family history positive for HTLV-I infection (2 patients [3.3%]). Thirty-three patients (55%) had a history of sexually transmitted diseases (STDs), with gonorrhea being the most frequently observed STD (in 18 patients [30%]), followed by syphilis (in 7 patients [11.7%]). Four patients (6.7%) had a history of herpes zoster, and 2 patients (3.4%) had received a diagnosis of leprosy in the past.

In the control group, there were 31 men (81.6%) and 7 women (18.4%). Concerning the age distribution of the control group subjects, 21 individuals (55.3%) were 21–40 years of age, 16 (42.1%) were 41–60 years of age, and 1 (2.6%) was >60 years of age. Twenty-three individuals (60.5%) were white, 8 (21.0%) were black, and 7 (18.4%) were mulattos. Patients and control subjects did not differ significantly in terms of mean age (51 years vs. 47 years, respectively).

Table 1 summarizes the main dermatological findings in the present study. Xerosis, cutaneous candidiasis, and palmar erythema were significantly associated with patients with HAM/TSP, compared with HTLV-I–negative control subjects. In contrast, pityriasis versicolor occurred significantly more frequently among subjects in the control group ($P < .05$). Xerosis (figure 1) was frequently associated with cutaneous atrophy, and, in general, a higher degree of xerosis could be correlated with a greater neurological disability (data not shown). Candidiasis also was a relatively frequent finding. Its main presentations were intertrigo and perianal candidiasis. Palmar erythema and malar erythema also occurred more frequently in the group with HAM/TSP, but they did not show any distinctive pattern that could differentiate them from erythema found in individuals with other diseases [24]. Skin biopsy was performed for

Table 2. Clinical and histopathological findings for 8 patients with a suggestive pattern of cutaneous lymphoma who underwent biopsy.

Patient	Sex, age in years	Dermatological finding	Skin biopsy
1	F, 55	Xerosis and intense cutaneous atrophy and scaling	Mononuclear lymphocytic infiltrate present in the upper (lichenoid pattern) and lower dermis; epidermotropism; and diffuse thickening of collagen fibers
2	F, 51	Xerosis, chronic eczema, intense seborrheic dermatitis, and palmar erythema	Lymphocytic infiltrate mainly around vessels of the papillary dermis; and epidermotropism
3	M, 48	Xerosis, seborrheic dermatitis, chronic eczema, candidiasis, and dermatophytosis	Diffuse lymphoid infiltrate in the upper dermis; epidermotropism was also detected in the follicular epithelium; slight fibroplasia in the papillary dermis
4	M, 48	Intense erythroderma and photosensitivity	Dense bandlike mononuclear infiltrate present in the upper dermis and around superficial vessels; epidermotropism; and some eosinophils present
5	M, 58	Xerosis, mild photosensitivity, and warts	Abnormal lymphocytes in the epidermis and papillary dermis; basal-layer hydropic degeneration; and slight epidermotropism
6	M, 56	Xerosis, intense photosensitivity, and candidiasis	Foci of lymphocytes, seen in the epidermis and in the upper dermis in a bandlike fashion
7	F, 65	Intense xerosis, palmar erythema, and trophic ulcers	Hyperkeratosis and acanthosis; and superficial cellular infiltrate seen around vessels and in some papillary bodies (figure 4)
8	M, 48	Xerosis, seborrheic dermatitis, and chronic eczema	Mononuclear cell infiltrates located in the upper dermis, around vessels, and in the interstitium; slight epidermotropism; and mild edema and fibrosis in the upper dermis

2 of these patients, and the results showed a nonspecific lymphocytic and histiocytic infiltrate around the vessels.

Although they were not significant in the case-control comparison, other common abnormalities detected in the present series were dermatophytosis and seborrheic dermatitis. The most frequent dermatophytoses were onychomycosis of the hallux nail and intertrigo of the feet. Seborrheic dermatitis showed the usual pattern and was confirmed by skin biopsy. Severe seborrheic dermatitis, similar to those forms of dermatitis found in patients with AIDS, was detected in only 1 patient (figure 2).

Scabies was found in 3 patients (5%). One of these individuals presented with papuloerythematous lesions on the face; scaly patches and hematic crusting involving the scalp, neck, and ears; and papuloerythematous lesions, which appeared in a follicular pattern, on the abdomen, thighs, and soles, with extensive peeling and crusting (figure 3). There was intense itching restricted to the scalp. Crusted scabies was diagnosed on the basis of the results of a skin biopsy that showed numerous *Sarcoptes scabiei* specimens. Eight (25%) of the 32 biopsies revealed a suggestive pattern of cutaneous T cell lymphoma (CTCL) [25, 26] (table 2 and figure 4). Although all of these patients exhibited extensive skin involvement, no specific clinical pattern was evident in this group. Table 2 summarizes the clinical and histopathological findings for these 8 patients.

Discussion. The present series is the first controlled study dealing with dermatological findings for a large group of patients with HAM/TSP. It shows that dermatological abnormalities, such as xerosis, dermatophytosis, candidiasis, and erythema, are more common in patients with HAM/TSP than was previously thought. In these patients, dermatological findings, although frequent, seem to be less severe than those seen in association with ATLL as well as those seen in association with HIV infection. In addition, lymphomatous infiltration of the skin could be observed in a significant proportion of patients with HAM/TSP. In our series, 25% of skin biopsy specimens showed a histopathological pattern similar to CTCL. The occurrence of CTCL and HAM/TSP in the same individual has been infrequently reported in the literature [25–27]. There was no specific clinical pattern that could suggest lymphomatous infiltration of the skin in the present series (table 2). For this reason, to investigate the real significance of such findings and to allow for a prospective evaluation of these individuals, skin biopsy could be justified for patients with HAM/TSP, even in the absence of a classical clinical presentation of CTCL.

The findings of the present study confirm previous findings that reported xerosis to be the main dermatological manifestation of HAM/TSP. Some authors have speculated whether such findings could be the result of hypohidrosis secondary to the involvement of the autonomic nervous system or of a direct effect of HTLV-I–infected cells at the epidermic level [27]. Recent studies by our group have demonstrated that the sympathetic skin response is significantly decreased in patients with HAM/TSP, compared with control subjects, indicating the fre-

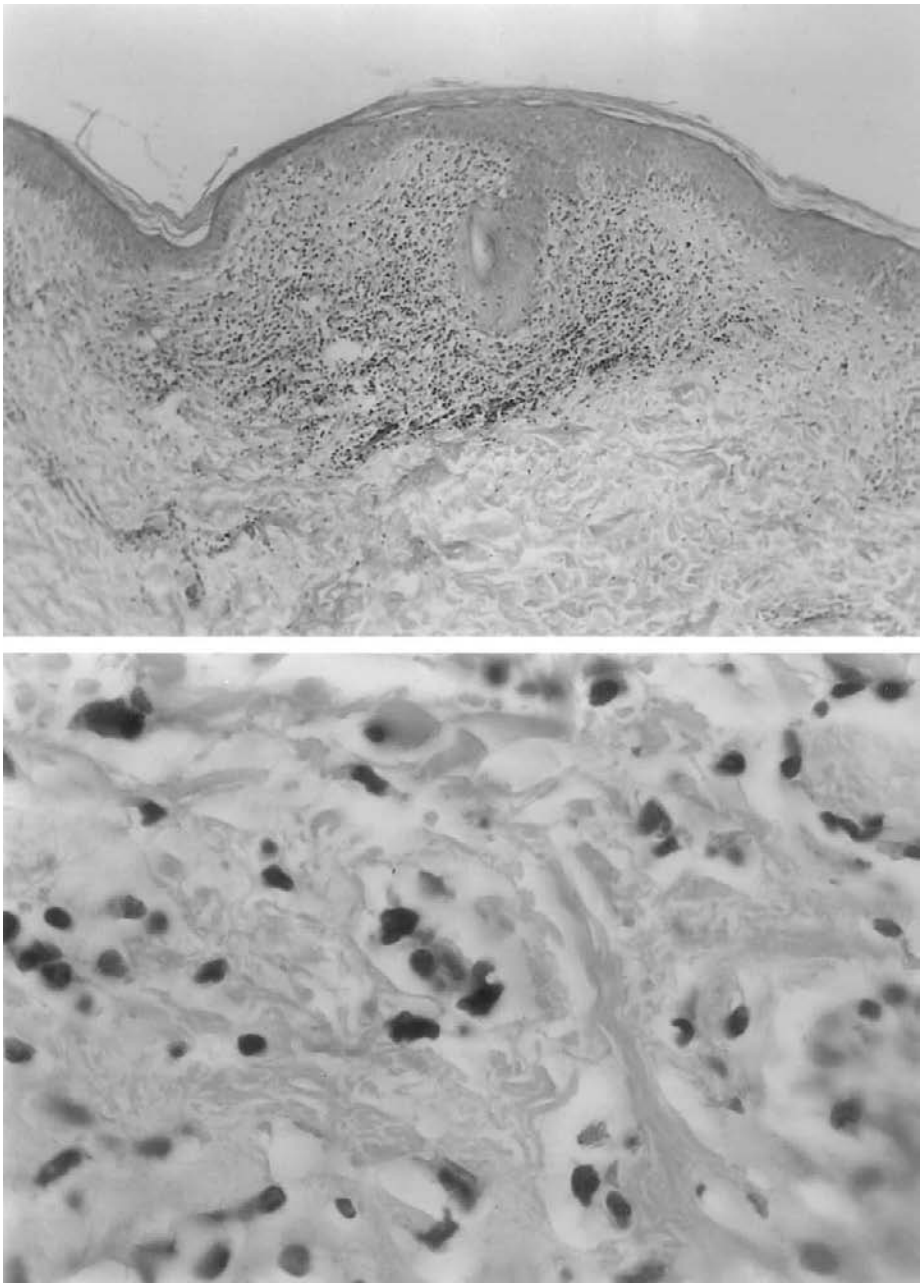

Figure 4. *Top,* Lymphoid cells in the superficial dermis, some of which extend to the epidermis and to the follicular epithelium (hematoxylin-eosin stain; original magnification, ×100). *Bottom,* Atypical lymphoid cells at the superficial dermis (hematoxylin-eosin stain; original magnification, ×1000).

quent involvement of the autonomic nervous system in these individuals [28]. Conversely, xerosis could still result from direct damage of the skin by infected lymphocytes. Some of the findings reported in the present study could result from the physical impairment posed by the neurological disease as a result of the myelopathy, and most of them worsened as the neurological disability progressed.

As already reported in the literature, candidiasis frequently has been found in patients with sphincter disturbances. Palmar and malar erythema, which has already been described in patients with HAM/TSP [27], is also reported in association with many other systemic diseases and may also occur in healthy people [24]. Chronic eczema is generally related to the neurological deficit in this specific population. Eczema can be found in the arms of patients that use walking sticks and in the hips of those patients restricted to a wheelchair. Regarding seborrheic dermatitis, many patients reported worsening of the symptoms and, eventually, the appearance of facial lesions after

the onset of HAM/TSP. Other subsets of dermatological manifestations in patients with HAM/TSP include diseases that are often associated with immunological disturbances, such as crusted scabies, which occurs in patients in whom the immune response to the parasite is diminished [29].

Concerning other abnormalities found in the present series, folliculitis decalvans, described elsewhere [30], is a rare skin disease of uncertain origin that is very resistant to treatment. Livedo reticularis, vitiligo, and erythema nodosum, although found in healthy people, can also be associated with cell-mediated immunity disorders [29]. These skin abnormalities may be the expression of an immunosuppression observed in HTLV-I–infected individuals [30–33]. Therefore, they can be classified as immune-mediated disorders.

In summary, the findings of the present study suggest that the skin is a frequently damaged organ in HTLV-I–infected individuals. This is not restricted to patients with ATLL but also can be frequently found among HTLV-I–infected patients with the immunologically associated neurological disease HAM/TSP. Skin involvement in patients with HAM/TSP may be classified as nonspecific lesions (xerosis, seborrheic dermatitis, and palmar erythema and eczema), infectious lesions (dermatophytosis, candidiasis, scabies, herpes zoster, and folliculitis), immune-inflammatory–mediated lesions (infective dermatitis, livedo reticularis, erythema nodosum, and vitiligo), or premalignant or malignant lesions (erythroderma and cutaneous lymphoma).

The dermatological finding most frequently found in the present series, xerosis, is that found most frequently in previously published reports. Many of the skin alterations associated with immunosuppression suggest that in these patients, the immune abnormality is not restricted to the nervous system itself. The frequent finding of lymphomatous infiltration restricted to the skin in patients with HAM/TSP is of importance because, for these individuals, disease may evolve to full-blown ATLL in the future. In addition, the follow-up of patients with possible malignant skin involvement would clarify several aspects of the natural history of HTLV-I infection. Would these patients eventually have systemic malignancy develop? Is there any correlation between this finding and the neurological impairment? More extensive and prospective studies are necessary to confirm these hypotheses.

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