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Histopathological and immunohistochemical studies of infective dermatitis associated with HTLV-I

Infective dermatitis associated with HTLV-I (IDH) is a chronic, recurrent, exudative eczema occurring in childhood which is considered to be a risk factor for the development of lymphoma and HTLV-I-associated myelopathy/tropical spastic paraparesis. Skin biopsies from 19 patients with IDH were studied histologically and immunohistochemically using the following antibodies: anti-CD3, CD45RO, CD20, CD79a, CD4, CD8, CD56, CD57, TIA-1, granzyme-B, and perforin. A chronic dermatitis similar to atopic and seborrheic dermatitis was observed in 15 cases, whereas architectural aspects mimicking mycosis fungoides were observed in the remaining four. The infiltrate consisted predominantly of CD8+ lymphocytes and of CD57+ cells in the dermis and epidermis. TIA-1 and granzyme-B were expressed in 15/18 cases and 5/19 cases at the proportion of ≤ 15% and ≤ 3%, respectively. All cases were negative for perforin and CD56. Like other dermatites, histologically IDH may represent a benign simulator of mycosis fungoides. IDH shows a predominance of CD8+ cells and a low percentage of cells with cytotoxic granules, indicating that most CD8+ lymphocytes are not activated. These findings differ from the immunohistochemical pattern of atopic and seborrheic dermatitis, possibly representing additional means of differentiation between IDH and these dermatites. The distribution of CD57+ cells suggests that they play a role in the inflammatory process.

Key words: HTLV-I infection, infective dermatitis, inflammatory simulators of mycosis fungoides, pediatric HTLV-I-associated myelopathy/tropical spastic paraparesis

Carriers of human T-cell lymphotropic virus type I (HTLV-I) may develop many diseases such as adult-T cell leukemia/lymphoma (ATL), an aggressive form of T-cell lymphoma, HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a chronic neurological disease and infective dermatitis associated with HTLV-I (IDH), a severe form of childhood infected eczema [1].

IDH was described in Jamaica in 1966 by Sweet [2] but only in 1990 was it related to HTLV-I [3]. Most cases have been reported in Jamaica [3, 4] but some have been reported in Colombia, the Dominican Republic, Trinidad-Tobago, and among Haitians resident in Miami [5-8]. In Brazil, one case of IDH was reported in Rio de Janeiro [9]. In Japan, where the frequency of HTLV-I carriers is high, only two cases of IDH have been reported [10].

IDH is associated with a non-virulent *Staphyloccus aureus* or beta-hemolytic *Streptococcus* infection of the skin and nasal vestibules, and involves mainly the scalp, external ear and neck. Conjunctivitis has been observed in most cases [5]. This disease is considered to be a risk factor for the development of ATL and HAM/TSP [11-14].

Since some infected children may eventually present other kinds of eczema, it is important to discriminate between IDH and atopic or seborrheic dermatitis, with the differential diagnosis being based on clinical features [5]. The differential diagnosis with seborrheic dermatitis is a source of concern mainly in puberty [15] but in the majority of IDH cases the lesions begin earlier.

In the present investigation, we studied the histopathological and immunohistochemical patterns of 19 patients with IDH in order to determine if they differ from atopic and seborrheic dermatitis and if they present histological aspects of cutaneous lymphoma.

Material and methods

Patients

The study group consisted of 19 children, 10 girls and 9 boys, 10 of them mulattos and 9 blacks, all of very low social status. The age at diagnosis ranged from 2 to 14 years (mean: 8.00 ± 3.63 years) in 18 children and was undefined in one child who had been abandoned. According to mothers' information, age at the onset of symptoms ranged from 2 months to 6 years (1.94 ± 1.74 years) in 18 children. All patients fulfilled the major criteria for the diagnosis of IDH [5]. Dermatological examination revealed extensive crusty

and erythematous lesions, miliary follicular papules, and retroauricular fissures. Disseminated scaly and erythematous papules or plaques were also observed in seven cases. The preferential sites of involvement were: scalp (100%), retroauricular areas (100%), neck (87%) and external ears (83%). In 10 cases the disease was more severe, involving all the segments of the body. Blepharoconjunctivitis was observed in 10/19 cases. The patients presented mild to moderate pruritus. All were treated with sulfamethoxazole/trimethoprim, with disappearance or marked improvement of the lesions but with relapses occurring when the medication was discontinued. The recurrent lesions were less severe and more localized. Patient follow-up ranged from 0.5 to 7 years (median: 3.35 years). In the four cases histologically mimicking mycosis fungoides (MF), follow-up ranged from 1 to 7 years (median: 3.7 years). No patient presented clinical evidence of lymphoma during follow-up (Oliveira, personal communication) but five of the children developed HAM/TSP during follow-up (Chagas, personal communication) [14].

Serological diagnosis

Antibodies to HTLV-I/II were investigated by diagnostic enzyme-linked immunosorbent assay (ELISA - Cambridge Biotech, Worcester, MA, USA) and confirmed with a Western blot capable of discriminating between HTLV-I and HTLV-II (HTLV Blot 2.4, Genelab, Singapore). Serologic assays for HIV were also performed. All patients were serologically positive for HTLV-I and negative to HTLV-II and HIV.

Histopathological and immunohistochemical studies

Punch skin biopsies were performed in the scalp lesion of all patients and in one case a biopsy was simultaneously obtained from a papular lesion of the abdomen. The biopsies were fixed in 10% buffered formalin, the blocks were embedded in paraffin, and histological sections were stained with hematoxylin and eosin (HE). The immunohistochemical study of the inflammatory cells was performed in paraffin-embedded sections using a panel of antibodies and a standard streptavidin-biotin-peroxidase technique [16]. The following immunohistochemical markers were employed: T-cell markers CD45RO, CD3, CD8 (Dako, Glostrut, Denmark), and CD4 (Novocastra, New Castle, UK); B-cell markers CD20 and CD79a (Dako) and NK cell markers CD56 and CD57 (Dako). The immunophosphatase technique (Streptavidin Biotin System) for identification of cytotoxic granules was performed using the anti-granzyme B, anti-perforin (Novocastra) and anti-TIA-1 (Immunotech, Marseille, France) antibodies. The cell count was made using a semi-quantitative assessment. The percentage of CD4+, CD8+ and lymphocytes with cytotoxic granules in the inflammatory infiltrate was calculated by counts on five high magnification fields (640X). The study was approved by the Research Ethics Committee of Hospital Professor Edgard Santos and informed consent was obtained from the children's mothers or from the persons responsible for the children.

Flow cytometry

Fifty microliters of whole blood was mixed with an equal volume of 1% BSA plus 0.1% sodium azide in PBS and incubated for 30 min on ice with antibodies against CD4 and CD8 and the corresponding isotype controls (Coulter-Immunotech). After incubation, erythrocytes were lysed using a simultaneous fixation and lysis solution (Becton-Dickinson). A minimum of 10,000 events per sample were acquired with a FACSort flow cytometer (Becton-Dickinson) and analyzed using the CellQuest software.

Results

Hyperkeratosis and/or parakeratosis with crusts and acanthosis of varying degrees were observed in all cases. The acanthosis was psoriasiform in six biopsies. Mild spongiosis was observed in 10 cases and spongiosis of moderate degree in one. Focal vacuolar degeneration of the basal layer and pigmented incontinence were observed in 16 cases. Five cases presented subcorneal pustules and seven presented collections of degenerated neutrophils within the stratum corneum (Munro-like abscesses). Lymphocytic epidermotropism was mild in 11 cases and moderate in four. Small collections of typical lymphocytes were seen within the epidermis (Pautrier-like abscesses) *(figure 1)* in four cases, associated with a minor degree of spongiosis or without spongiosis. Focal obliteration of the basal layer was seen in five cases, being of moderate degree in two of them *(figure 2)*. A linearly arranged layer of single cells in the epidermal basal layer was seen in two cases. In the dermis, a mild to moderate infiltration consisting predominantly of lymphocytes was observed in 18/19 cases and in

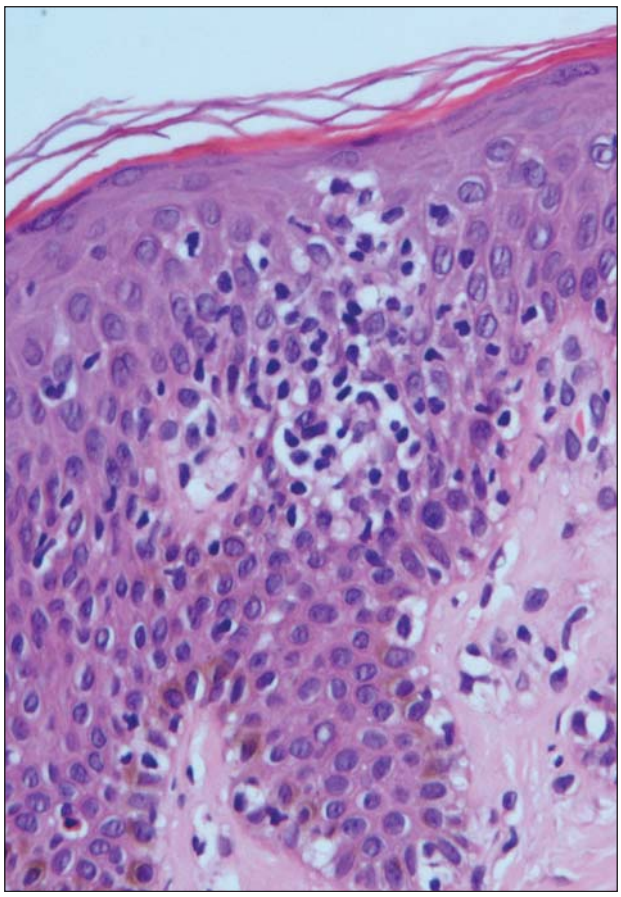

Figure 1. Epidermis with small collections of lymphocytes (Pautrier-like abscess). HE, A 200.

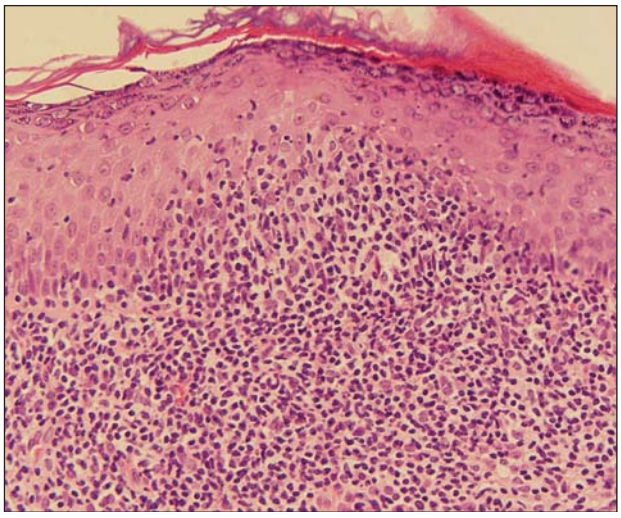

Figure 2. Observe the presence of a heavy dermal lymphocytic infiltration causing basal obliteration. HE, A 160.

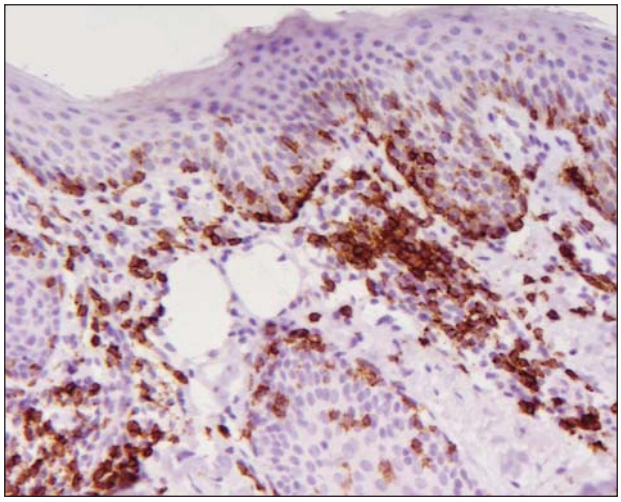

Figure 3. CD8+ lymphocytes are seen in the dermis and along the epidermal basal layer. CD8. A125.

one it was of marked degree *(figure 2)*. Plasma cells, neutrophils and rare eosinophils were also observed. The pattern of dermal infiltration was lichenoid in 10 biopsies, and superficial perivascular and periadnexial in the others. In two biopsies a mid-dermis perivascular infiltration was observed associated with the superficial perivascular pattern. The biopsy of the papule presented a moderate lymphocytic infiltration associated with a moderate epidermotropism of lymphocytes, a small Pautrier-like abscess and linearly arranged single lymphocytes along the basal layer of the epidermis. The aspects observed were similar to those detected in the biopsy from the scalp of the same patient.

The infiltrate consisted predominantely of CD3+ and UCHL-1+ T cells in all scalp biopsies and in the papular lesion. In six cases B cells (CD79a+ and CD20+ cells) were also observed. The percentage of CD8+ and CD4 + cells varied from 53% to 94% and from 4% to 26% respectively but in one case the percentage of CD4+ cells was higher (42%) *(table 1)*. The epidermal infiltrating lymphocytes were CD8+ *(figure 3)*. Fifteen of 18 cases were positive for TIA-1 and 5/19 for granzyme B. The frequency of TIA-1 expression ranged from 0.7% to 15% and the frequency of granzyme B expression ranged from 0.5% to 3%. CD57+ cells were observed in 17/18 cases, corresponding to 0.6% to 17.5% of the inflammatory cells. In five cases with basal obliteration, CD57+ cells were seen at the dermo-epidermal junction *(figure 4)* or within the epidermis. No CD56+ or perforin+ cells were observed in the 19 patients studied. As shown in *table 1*, CD4 and CD8 levels in peripheral blood were highly variable in the seven patients evaluated (from 25.3 to 48.0, and 19.2 to 30.8, respec-

Table 1. Amount of CD4+ and CD8+ lymphocytes in blood and skin lesions

	Blood CD4+ (%)	Blood CD8+ (%)	Blood CD4/CD8	Skin lesions CD4+ (%)	Skin lesions CD8+ (%)
1	48.00	25.16	1.9	11.6	86
2	25.32	19.28	1.31	11	80
3	-	-	-	10	73
4	-	-	-	7	53
5	38.85	22.34	1.74	11	81
6				4.6	90
7	40.87	27.06	1.51	10	82
8	-	-	-	5	86
9	-	-	-	8	88
10	40.48	30.56	1.32	8.5	80
11	45.89	29.53	1.56	4	94
12	-	-	-	8	57
13	-	-	-	14	83
14	-	-	-	6.5	64
15	-	-	-	6	81
16	-	-	-	20	78
17	-	-	-	26	72.5
18	-	-	-	42	56
19	46.09	30.88	1.49	10	60

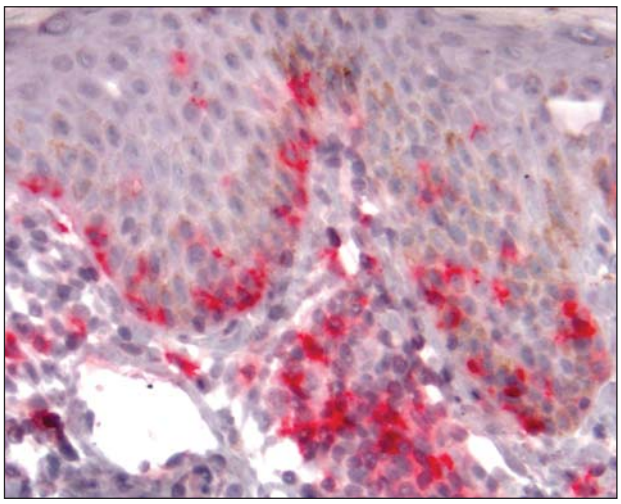

Figure 4. CD57+ lymphocytes are seen in the dermis, along the basal layer and within the epithelial layer of a hair follicle. CD57. A200.

tively). However, CD4/CD8 ratios were within the normal range (1.47 ± 0.11, n = 7).

Comments

The present study was conducted on children born in Salvador, Bahia, a city in Northeast Brazil with 1.76% of HTLV-I infection in the general population [17].
The histopathological evaluation of the 19 skin biopsies obtained showed a chronic dermatitis similar to the pattern described for atopic dermatitis, seborrheic dermatitis and IDH in 15 cases [5, 18, 19]. However, architectural aspects mimicking the patch stage of MF were observed in four cases, i.e., collections of a few lymphocytes within the epidermis (Pautrier-like abscess), lymphocytic epidermotropism, and/or basal obliteration by lymphocytes, sometimes with a linear array of lymphocytes along the basal layer of the epidermis [20-22]. This pattern was associated with a moderate or marked lymphocytic infiltration in the superficial dermis, but no atypical lymphocytes or mitoses were observed. These features are not generally described in atopic or seborrheic dermatitis [15, 18, 19].
The diagnosis of the patch stage of MF is frequently difficult. Some investigators state that this diagnosis can be based exclusively on architectural aspects [20-22], whereas others believe that only the presence of atypical cells constitutes a highly reliable feature for the diagnosis of MF because the architectural aspects in question can be found in biopsy specimens of benign simulators of MF [23, 24].
The lesions of the present patients disappeared or showed great improvement during the use of sulfamethoxazole/trimethoprim and, after drug withdrawal, recurrent lesions were always less severe and more localized. The patients with architectural aspects mimicking MF have been followed-up for one or more years (median: 3.75 years) and their lesions have disappeared or improved, showing that these are benign simulators of this kind of lymphoma. It is important to make a correct differential diagnosis because ATL may present, infrequently, the histopathological pattern of MF [25, 26]. Besides, MF may occasionally occur in childhood and puberty [27, 28].
In atopic and seborrheic dermatitis, T lymphocytes are predominantly of helper cell phenotype [29-34]. Most of the present cases (18/19) showed infiltrates predominantly consisting of CD8+ cells, possibly indicating a different pathogenic mechanism. The predominance of CD8 cells in the skin biopsies could not be attributed to an inversion of CD4/CD8 ratios in blood, since in parallel blood samples from seven cases CD4/CD8 ratios were normal (1.47 +/– 0.11, n = 7), as shown in *table 1*.
It is known that granule exocytosis mediated by perforin/granzyme represents the main pathway of CD4 and CD8 T cell cytotoxicity in humans [35]. The expression of cytotoxic molecules TIA-1 and granzyme B in a small percentage of cells and the absence of perforin-positive cells indicate that the majority of CD8+ cells were not cytotoxic cells but possibly suppressor cells. TIA-1 was the most frequent cytotoxic molecule observed in the present cases. TIA-1 is a cytolytic granule-associated protein that may define a subpopulation of CD8+ T lymphocytes possessing cytolytic potential but is not related to activation [36] like granzyme and perforin. In contrast to atopic dermatitis, activated cytotoxic T cells were rare or absent in the patients studied [35].
CD57+ cells may represent a T cell subset that increases in some conditions such as acquired immunodeficiency, rheumatoid arthritis, and after organ transplantation, but that is rare in children [37]. These cells were seen in the majority of the present cases, even within the epidermis or obliterating the basal layer. It has been reported that CD57+ T cells produce larger amounts of interferon-γ than normal T-cells [38]. The distribution of CD57+ cells suggests that they play a role in the inflammatory process.
No histological or immunological differences were observed between the scalp and the papular lesions, indicating that the latter are part of the same process. The predominance of CD8+ cells, the absence of perforin+ cells and the presence of rare granzyme B+ cells differ considerably from the immunohistochemical findings of atopic and seborrheic dermatitis [35], possibly representing additional means of differentiation between IDH and these dermatites. ■

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