Infective Dermatitis Associated with HTLV-1 Mimics Common Eczemas in Children and May Be a Prelude to Severe Systemic Diseases

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KEYWORDS
- Infective dermatitis • Atopic dermatitis • Seborrhoeic dermatitis • HTLV-1 infection
- Adult T cell leukemia/lymphoma (ATLL)

KEY POINTS
- The variable clinical presentation of IDH, in particular its chronicity, the morphology and distribution of the lesions, and its clinical resemblance to other cutaneous inflammatory conditions, make it hard to distinguish from other common dermatoses.
- It is important to know which factors lead only some infected children to develop IDH and how to prevent the progression of IDH to HAM/TSP and adult T-cell leukemia/lymphoma (ATLL), which in some areas occurs very early.
- Considering that IDH and ATLL occur through vertical transmission of HTLV-1, it is important to prevent this route of transmission.

INTRODUCTION
Human T-cell lymphotropic virus type 1 (HTLV-1), the first isolated human pathogenic retrovirus, was discovered independently in Japan and the United States. In Japan in 1977, Uchiyama and colleagues\textsuperscript{1} described a human malignant disease termed adult T-cell leukemia/lymphoma (ATLL). Three years later, in 1980 in the United States, the identification of the first human retrovirus was reported, human T-cell leukemia virus type-1 (HTLV-1) in a patient with cutaneous T-cell lymphoma.\textsuperscript{2} Concurrently, the virus was also isolated by Yoshida and colleagues\textsuperscript{3} and was termed adult T-cell leukemia virus (ATLV). Soon, HTLV and ATLV were shown to be identical at the sequence\textsuperscript{3} level and have since been named HTLV type 1.\textsuperscript{4} Subsequent molecular studies confirmed HTLV-1 as the etiological agent for ATLL\textsuperscript{5} and that the virus encodes a 40-kDa cell-transforming oncoprotein named Tax (Transactivator X).\textsuperscript{4} Later, another HTLV was isolated, human T-cell lymphotropic virus type-2 (HTLV-2).\textsuperscript{6} Both viruses are similar in 66% of their genome sequences and because of this, there are serologic cross-reactions between them. HTLV-2 has not been consistently linked with any given pathology; however, there are few publications that have related it to neurologic diseases.\textsuperscript{7}

THE ORIGINS OF HTLV-1
HTLV-1 infection in humans may have had more than one origin. The major origin is thought to be...
in equatorial Africa in primates and chimpanzees carrying a virus closely related to HTLV-1. It is likely that this represents the source of virus in descendants of people who came to the Americas (the Caribbean Islands, United States, and South America) from Africa. There is also evidence that the virus could have come to Japan with European voyagers and travelers who took with them people and primates from Africa. As discussed further below, HTLV-1 varies little when contrasted with HIV. Nonetheless, there are variants that exist within populations. Variants from humans are closely related to variants of African chimpanzees.

**GEOGRAPHIC SUBTYPES**

Six different genetic subtypes of HTLV-1 have been proposed based on phylogenetic analyses: a, or Cosmopolitan, which is distributed worldwide; b, from Central Africa; c, a highly divergent Melanesian strain from Papua Guinea and Australia; d, isolated from Central African Republic pygmies, and from 2 patients in Cameroon and Gabon; e, isolated in a single sample from an Efe pygmy in the Democratic Republic of Congo; and subtype f, detected in an individual from Gabon. The most widespread and best studied subtype, Cosmopolitan, is further divided into 5 subgroups based on geographic distribution: (A) Transcontinental, (B) Japanese, (C) West African/Caribbean, (D) North African, and (E) Black Peruvian. The most widespread (with a worldwide distribution) and best studied is the Cosmopolitan subtype A (HTLV-1 a), which is also the strain prevalent in South Africa. There is no association between the subtypes and clinical manifestations.

**HTLV-1 TRANSMISSION**

Modes of transmission are shared between the HTLVs and HIVs. Transmission typically occurs horizontally through blood contact, including the transfusion of infected cellular products or the sharing of needles and syringes, but also sexually through the transfer of contaminated body fluids. Vertical transmission occurs primarily during breastfeeding and only rarely in utero. The efficiency of the mother-to-child transmission route is estimated to be 20% and has been correlated with individual variables, such as HTLV-1 proviral load, the concordance of HLA class I type between mother and child, and the duration of breastfeeding. Mother-to-child transmission during the intrauterine period or peripartum has been reported to occur in fewer than 5% of cases.

Similar to other sexually transmitted infections, sexual transmission of HTLV-1 is associated with unprotected sex, multiple sexual partners, lifetime contact with an HTLV-1–infected partner, the presence of genital sores or ulcers, and paying or receiving money for sex. The route of infection has been shown to be related to the development of specific diseases associated with HTLV-1. For example, ATLL has been associated with breastfeeding and HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) with blood transfusion and breastfeeding. Rare cases of posttransfusion ATLL have been described. The risk of HTLV-1 transmission by transfusion varies with the prevalence of the virus in the general population, as well as in blood donors. The time interval before seroconversion is also another important variable that interferes with the calculation of the residual risk of transmission. In the case of transfusion-transmitted HTLV-1, the window period usually varies between 41 and 65 days but may be longer.

**CLINICAL CHARACTERISTICS OF HTLV-1 INFECTION**

The most widely known clinical entities associated with HTLV-1 are ATLL, HAM/TSP, HTLV-1–associated uveitis (HAU), and infective dermatitis associated with HTLV-1 (IDH). Most infected individuals remain asymptomatic throughout life, aptly named asymptomatic carriers (ACs). Generally, it is considered that only 2% to 5% of infected individuals develop an HTLV-1–related clinical disorder. Notwithstanding, there is increasing evidence that HTLV-1 infection is responsible either directly or indirectly, for a variety of other diseases, including arthropathy, periodontal disease, sicca syndrome, Sjögren’s syndrome, polymyositis, lymphocytic alveolitis, and a large number of neurologic deficits. It is particularly striking that these findings occur in a large group of individuals traditionally considered to be asymptomatic HTLV-1 carriers, indicating that morbidity associated with HTLV-1 is much higher than has been generally considered. HTLV-1 is an indolent virus with a long latency period between infection and development of disease. Individuals infected by HTLV-1 are more susceptible to other infections, such as tuberculosis and other bacterial infections, viral infections, and superficial mycoses. They also present frequently with parasitoses, such as scabies, including crusted scabies and strongyloidiasis, with a high risk of disseminated strongyloidiasis.
DIAGNOSIS OF HTLV-1 INFECTION

The most commonly used method for the diagnosis of HTLV-1 infection is serology and the most used serologic screening test is the enzyme-linked immunosorbent assay (ELISA). Samples that repeatedly test positive in the ELISA must be retested in an immunoblot assay for serologic confirmation so as to distinguish between HTLV-1 and HTLV-2. The preferentially used immunoblot assay is the highly sensitive Western blot 2.4. Cases that do not meet the criteria for HTLV-1 or HTLV-2 positivity are considered indeterminate. In these cases, molecular testing should be carried out, polymerase chain reaction (PCR) being the most commonly used method capable of clarifying indeterminate serologic status. This method may even detect infection in individuals who were defined as seronegative but who had a clinical status suggestive of HTLV-1-associated disease. PCR is also used to detect DNA in tumor tissues and in other biologic specimens.

IMMUNE CONTROL OF HTLV-1 INFECTION

HTLV-1’s lifelong persistence in CD4+ lymphocytes determines a prolonged interaction between the virus and the immune system, which may ultimately result in a broad spectrum of associated diseases. The immunopathogenic mechanism behind this may be related to the direct action of the virus on the immune system or a consequence of the response of the immune system to the virus. Instead of immunosuppression, HTLV-1 infection causes dysregulation of the immune system with spontaneous lymphoproliferation and increased T-cell activation. Unstimulated cells from asymptomatic HTLV-1 carriers have been shown to secrete high levels of Th1 and Th2 cytokines, such as tumor necrosis factor alfa (TNF-α), interferon-γ (IFN-γ), and interleukin (IL)-5 and IL-10, compared with cells from seronegative individuals. Moreover, it has been found that CD4+ lymphocytes represent the principal source of IFN-gamma and that high levels of IL-10 are able to down-regulate the exacerbated Th1-type immune response that occurs in these carriers.

Mechanisms underlying the persistence and pathogenesis of HTLV-1 remain largely unknown; however, factors thought to influence the outcome of HTLV-1 infection include the host’s immune response gene expression in host lymphocytes, the genomic integration site, and the sequence of the provirus.

The role of the innate immune response in persistent HTLV-1 infection is unclear. It seems that persistence of the virus in the skin or blood may be partly the result of the inadequate immune response. The question is, therefore, how much does the failed innate immune response influence the role and the extent to which the adaptive immune response responds to the presence of the virus.

There has been a longstanding debate on the question of whether HTLV-1 is latent or persistently expressed in vivo. Persistent expression, instead of latency, is slowly gaining acceptance. Speculation has it that HTLV-1 persists through an equilibrium “set point” of proviral HTLV-1, set by a balance between spontaneous proviral expression and cytotoxic T lymphocyte (CTL)-mediated immune surveillance. The variation in the set point among hosts referred to in the previous sections may be explained by 2 possible factors: the rate of proliferation of T cells in response to HTLV-1 expression driven mainly by Tax protein, and the rate at which CTLs kill HTLV-1–expressing cells. It has been observed that individual clones of infected cells can persist in patients for several years, indicating that the proviral load (PVL) is maintained in vivo mainly by infected cells undergoing mitosis during the chronic phase of infection. This leads to the hypothesis that infectious transmission of HTLV-1 is important early in infection across the virological synapse whereas mitotic replication is responsible for maintaining PVL once a persistent infection has been established and has reached equilibrium with the immune response.

In up to 5% of infected individuals, persistent clonal proliferation culminates in malignant transformation in ATLL. The leukemic clones generally carry only one (complete or defective) provirus per cell. Evidence has shown that within a given HTLV-1–infected individual, 2 features differentiate the clones of infected cells: the antigenic specificity of the T-cell clones (eg, T-cell receptors), and epigenetic modifications or the proviral insertion site in the host genome. Activation of the infected T cell by either antigen or cytokines (such as IL-2 or IL-15) might result in expression of the integrated provirus. Epigenetic changes in the infected cell affect the rate of proviral infection. The character of the genomic site appears to influence PVL expression, in turn resulting in simultaneously strong positive and negative selection of the T cell. The net effect determines the T cell’s survival in the host, and so its contribution to retroviral persistence.

IDH

IDH has been reported in the Caribbean area, Latin America, and in a few countries in Africa, including Senegal and South Africa. The first
description of this disease was by Sweet in 1966.20,46 This investigator recognized 17 patients from Jamaica that had a peculiar type of eczema generally starting at the age of 2 years, seldom before 18 months. The lesions were scaly, exudative, and crusted and distributed on nostrils, ears, face, scalp, and neck. Sweet also observed a generalized and fine papular eruption and the relapsing character of the lesions after withdrawal of antibiotics. In the following year, Walshe47 documented a high incidence of *Staphylococcus* and/or beta hemolytic *Streptococcus* (BHS) infection in the nose and skin lesions of 25 cases of infective dermatitis.5,47 It was postulated that these children might be immunosuppressed. In 1990, for the first time infective dermatitis was linked to HTLV-1 infection.48 This relationship was later confirmed in a study in which 50 patients with IDH were compared with 35 patients with atopic dermatitis (AD).20 Only 5 of 35 patients with AD were seropositive for HTLV-1. In both groups, microbiologic studies showed frequent colonization with *Staphylococcus aureus* and/or BHS. On comparing the blood count findings between the 2 groups, patients with infective dermatitis were anemic, had a higher white blood cell count and had a more elevated erythrocyte sedimentation rate than patients with AD. They also had a significantly higher incidence of abnormal serum proteins and dermatopathic lymphadenopathy.20 In this study, the disease was named as IDH and the major and minor criteria for the diagnosis were proposed. In a follow-up study of 42 infanto-juvenile IDH patients (Box 1).44 The following markers expand from La Grenade and colleagues’ original criteria.

1. No reference was made in La Grenade and colleagues’ criteria to the frequency of the affected areas and, as such, it is important to consider that the scalp is always involved. In Bahia, Brazil, besides the scalp, the retroauricular areas are also involved in 100% of the cases and in all patients at least 3 areas are affected.

2. Crusting of the nostrils was a common finding; however, this feature was absent in some patients, and it is an inconstant feature.

3. Rhinorrhea is a common symptom in children caused by several other diseases.

4. The relapsing nature of this disease with a prompt response to appropriate therapy and an equally rapid relapse if the drugs are withdrawn, was present in all the patients and should be considered as an indispensable criterion for diagnosis.

### Box 1

**Major criteria for the diagnosis of infective dermatitis associated with HTLV-1**

1. Presence of erythematous-scaly, exudative, and crusted lesions of the scalp, retroauricular areas, neck, axillae, groin, paranasal and perioral skin, ears, thorax, abdomen, and other sites

2. Crusting of nostrils

3. Chronic relapsing dermatitis with prompt response to appropriate therapy but prompt recurrence on discontinuation of treatment

4. Diagnosis of HTLV-1 infection (by serologic or molecular biologic testing)

Of the 4 major criteria, 3 are required for diagnosis, with mandatory inclusion of numbers 1, 3, and 4. To fulfill criteria 1, involvement of ≥ 3 of the sites is required, including involvement of the scalp and retroauricular areas.

**Abbreviation:** HTLV-1, human T-cell lymphotropic virus type-1.


5. The disease may begin later in childhood, and even in adulthood.

6. In some patients serologically negative for HTLV-1, PCR performed in peripheral blood mononuclear cells may be positive, and it is prudent to test when patients with the classic characteristics of IDH present negative serology.44

IDH has been correlated with vertical transmission and long-term breastfeeding.44,48 Furthermore, IDH may represent an early clinical marker for HTLV-1 infection and an indicator of increased risk for developing other, even more devastating HTLV-1–associated diseases.

### CLINICAL FINDINGS

The disease generally appears at 18 months but may occur earlier. In one study, in 37% of the patients the disease appeared at 12 months or earlier.44 The frequency of IDH is greater among female patients.20,44 IDH is a chronic and recurrent eczema occurring during childhood and infrequently in adolescence or adulthood. It is distinctive, often beginning with a rhinitis identified by the mother as a “cold.” This is followed by an oozing, weeping eruption on many body areas.49 The lesions are erythematous, scaly, frequently covered by yellow and fetid crusts always involving the scalp (Fig. 1), retroauricular
regions (Fig. 2), and many other areas (Figs. 3 and 4, Table 1), sometimes associated with other types of skin or mucosal lesions (Table 2). In one study, the lesions were disseminated in 83% of the patients. As previously referred, affected individuals have to fulfill the major criteria for a diagnosis to be made (see Box 1). S. aureus and/or BHS are generally cultured from the anterior nares or skin lesions. Patients who had no treatment for a period of more than 6 months and who presented no skin lesions are considered to be in remission. The mean age of complete remission of IDH is 15 years, varying from 10 to 20 years. However, IDH has been reported to persist until 23 years of age. It is important to emphasize that IDH may begin in adulthood with the same clinical and immunohistochemical characteristics of IDH at early onset. However, there are only 9 reported cases, all in female patients and 4 associated with HAM/TSP. Co-morbidities associated with IDH include scabies, corneal opacities, acquired ichthiosis, chronic bronchiectasis, glomerulonephritis, and lymphocytic interstitial pneumonitis.

**DIFFERENTIAL DIAGNOSIS**

The most important differential diagnosis of IDH is with AD (Table 3). A positive serology for HTLV-1, although helpful, is not the only criterion for diagnosis. Both diseases are susceptible to infection of the lesions by S. aureus; however, infection is more marked in IDH. A childhood onset is also shared by the 2 conditions but a significant
The difference between these conditions is the absence of family history of atopy in IDH, a feature that characterizes AD. Patients with both conditions complain of pruritus, even though the intensity is much less in IDH. Different from AD, patients with IDH always present severe lesions in the scalp and retroauricular regions, frequently with retroauricular fissures. On the other hand, the frequent findings of lesions in the antecubital and popliteal fossae may sometimes make it difficult the differentiate IDH from AD. The main differential diagnosis is clinical and is accessible to all dermatologists.

Differential diagnosis with seborrhoeic dermatitis (SD) is imperative only when the IDH begins in puberty, which occurs infrequently. SD is more common during or after puberty, the time during which IDH improves or disappears. Although there are some similarities, IDH has distinct clinical features that allow for it to be differentiated from SD (Table 4).

### Table 1
Distribution of lesions in 42 patients with infective dermatitis associated with human T-cell lymphotropic virus type-1 from Bahia, Brazil

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Scalp</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Retroauricular regions</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Neck</td>
<td>37 (88.1)</td>
</tr>
<tr>
<td>Axillae</td>
<td>35 (83.3)</td>
</tr>
<tr>
<td>Groin</td>
<td>33 (78.6)</td>
</tr>
<tr>
<td>Paranasal skin</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>Ears</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>Thorax</td>
<td>27 (64.3)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>26 (61.9)</td>
</tr>
<tr>
<td>Antecubital and popliteal fossae</td>
<td>24 (57.1)</td>
</tr>
<tr>
<td>Eyelids</td>
<td>24 (57.1)</td>
</tr>
<tr>
<td>Forehead</td>
<td>23 (54.8)</td>
</tr>
<tr>
<td>Perioral region</td>
<td>21 (50.0)</td>
</tr>
<tr>
<td>Umbilicus</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>Limbs</td>
<td>15 (35.7)</td>
</tr>
<tr>
<td>External genitalia</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Buttocks</td>
<td>7 (16.7)</td>
</tr>
</tbody>
</table>


### Table 2
Frequency of lesions in infective dermatitis associated with human T-cell lymphotropic virus in 42 patients from Bahia, Brazil

<table>
<thead>
<tr>
<th>Type of Condition</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythematous-scaly-crusty lesions</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Retroauricular fissures</td>
<td>32 (76.2)</td>
</tr>
<tr>
<td>Slightly erythematous-scaly papules</td>
<td>32 (76.2)</td>
</tr>
<tr>
<td>Crusting of nostrils</td>
<td>27 (64.3)</td>
</tr>
<tr>
<td>Fine papular rash</td>
<td>25 (59.5)</td>
</tr>
<tr>
<td>Blepharocconjunctivitis</td>
<td>24 (57.1)</td>
</tr>
<tr>
<td>Follicular papules</td>
<td>19 (45.2)</td>
</tr>
</tbody>
</table>


### PATHOLOGIC AND IMMUNOHISTOCHEMICAL FINDINGS

The pathologic aspects of IDH are similar to other types of eczema, such as AD and SD, predominantly being those of a spongiotic dermatitis of variable degrees of intensity or of a simple chronic dermatitis, depending on the duration of the biopsied lesion. Thus, pathology does not help in the differential diagnosis among IDH, AD, or SD. Infrequently, histology may mimic psoriasis or mycosis fungoides. Biopsies for immunohistochemical findings are important. In contrast to what is observed in AD and SD, in which the T lymphocytes are predominantly of the helper cell phenotype, in IDH the infiltrate is only or predominantly CD8 positive. Nevertheless, the CD8-positive lymphocytes are perforin negative and rarely granzyme-B⁺, suggesting that they are not activated cytotoxic T lymphocytes.

### DISEASE EVOLUTION

Epidemiologic data suggest that IDH is not only a marker of childhood HTLV-1 infection but also a possible harbinger of more serious HTLV-1-associated disorders. Reports indicate that IDH increases an individual’s risk for ATLL and HAM/TSP.
ATLL is an aggressive lymphoproliferative malignancy of peripheral T cells, with short survival in its acute form. It is classified into 5 clinical forms: acute, chronic, lymphoma, smoldering (leukemic and non-leukemic), and primary cutaneous tumoral. Its occurrence is associated with vertical transmission of HTLV-1 through breastfeeding. There are rare reports about progression of IDH to ATLL in puberty. It has been observed that 37.5% of cases of ATLL with cutaneous manifestations have had a history of severe childhood eczema involving the scalp that was suggestive of IDH. The mechanisms that lead to this development have not yet been elucidated. It is probable that both genetic factors of the host and external factors are involved.

Table 3
Different clinical characteristics of infective dermatitis associated with HTLV-1 and atopic dermatitis up to 18 months

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>IDH</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>From 18–24 mo onward</td>
<td>From 18–24 mo onward</td>
</tr>
<tr>
<td>Atopy</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Slight to moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Erythematous-scaly lesions with yellow crusts, papules, retroauricular fissures, and generalized fine papular rash</td>
<td>Erythematous and edematous papules and plaques, sometimes with vesiculation, generally replaced by lichenification</td>
</tr>
<tr>
<td>Distribution</td>
<td>Scalp, retroauricular areas, external ear, eyelids margins, perinasal skin, neck, axillae, and groin</td>
<td>Elbow and knee flexures, sides of the neck, wrists, ankles, and hands</td>
</tr>
<tr>
<td>Crusting on anterior nares</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Blepharoconjunctivitis</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; HTLV-1, human T-cell lymphotrophic virus type-1; IDH, infective dermatitis associated with HTLV-1.

Data from Refs. 19, 44, 52

Table 4
Different clinical characteristics of infective dermatitis associated with HTLV-1 and seborrheic dermatitis

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>IDH</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>From 18 mo onward</td>
<td>Puberty and adulthood</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Slight to moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Erythematous-scaly lesions with yellow crusts, papules, retroauricular fissures, and generalized fine papular rash</td>
<td>Erythematous greasy scaly lesions</td>
</tr>
<tr>
<td>Distribution</td>
<td>Scalp, retroauricular areas, external ear, eyelids margins, perinasal skin, neck, axillae, thorax, abdomen, and groin</td>
<td>Scalp; retroauricular areas; external ear; glabella; eyebrows; nasolabial folds; neck; presternal, interscapular, and submammary regions; axillae; groin; and umbilicus</td>
</tr>
<tr>
<td>Retroauricular fissures</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Crusting on anterior nares</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Blepharoconjunctivitis</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

Abbreviations: HTLV-1, human T-cell lymphotrophic virus type-1; IDH, infective dermatitis associated with HTLV-1; SD, seborrheic dermatitis.

Data from Refs. 19, 44, 53
Gabet and colleagues studied the HTLV-1 replication over 2 years in a patient with IDH associated with strongyloidiasis. They believe that this parasitosis may predispose HTLV-1 carriers to develop ATLL. They observed elevated PVL together with persistent oligoclonal expansion of the infected lymphocytes. The replication pattern was very different from that observed in asymptomatic carriers, being more similar to the pattern found in ATLL.

HAM/TSP is a myelopathy characterized by slowly progressive spastic paraparesis that may cause mild sensory involvement and bladder disturbances. Even though HAM/TSP has been characterized as an adult-onset disease, several cases with early-life onset have been described, most of them associated with IDH. Among 36 cases of IDH with continued follow-up, 17 progressed to HAM/TSP in childhood or adolescence. There is a great familial clustering among cases of IDH and of juvenile HAM/TSP. Recently, clustering of IDH and/HAM/TSP was shown in 15 families observed among 28 families with IDH, of which 93% of the cases occurred in 2 generations. With the exception of 2 mothers of children with IDH, all the mothers with HAM/TSP had at least one child with HAM/TSP.

**PATHOGENESIS**

HTLV-1 PVL is a major determinant of disease development in infected individuals and is considered to remain stable over time. The rate of HTLV-1 proviral expression has been shown to correlate with the outcome of infection. PVL is higher in adulthood HAM/TSP and ATLL in relation to asymptomatic carriers. It has also been observed that the HTLV-1 PVL is significantly higher in patients with IDH than in asymptomatic carriers and is similar to that found in patients with HAM/TSP.

According to Gillet and colleagues, the significantly higher PVL in IDH, also observed in carriers with strongyloidiasis, was due to an increase in the mean clone abundance, and not due to an increase in the number of infected clones.

Patients with IDH produce larger quantities of TNF-α and IFN-gamma than HTLV-1 carriers and are able to modulate IFN-gamma production when anti–IL-15 is added. However, anti–IL-2 was not able to significantly reduce the immunologic response in these patients. These data indicate that IDH is characterized by an exaggerated, type-1 immune response. Furthermore, no difference was observed between mRNA in IDH and controls, which supports the findings that an immunologic response in IDH differs from AD and that a type-2 immune response is not responsible for the tissue damage observed in IDH. The similarities between the immunologic response in patients with IDH and HAM/TSP and the high PVL observed in IDH provide support that IDH is a risk factor for development of HAM/TSP. TFN-α has been associated with pathology of chronic inflammatory and autoimmune diseases and may be, at least in part, responsible for the marked inflammatory aspect of IDH lesions.

Currently, little is known about the mechanism by which IDH is followed by ATLL later in life in some patients. It is possible that the presence of viral antigens and bacterial superantigens may stimulate the lymphocytes, increasing the number of target cells available to be infected by HTLV-1. With this expansion of infected T-cells, activation signals and growth factors are produced for uninfected T-cells and repeated clonal expansion of these cells increases the chance of the additional events required for transformation and leukemogenesis. Recently published data reveal that both the proviral integration sites and the oligoclonality index differ between patients with IDH and those with ATLL. Atypical T cells, including flower cells, have been found in peripheral blood smears of 35% (11/31) of patients with IDH (children and adolescents). These cells can be found in adult HTLV-1 carriers considered to be at high risk for developing ATLL. Flower cells are commonly found in the acute-type of ATLL and occasionally in the chronic and smoldering types. Moreover, proviral monoclonal integration was detected in 7 of those 11 patients with IDH with atypical cells in peripheral blood but analysis of T-cell receptor gene rearrangements revealed a polyclonal population of T cells. Furthermore, they cannot be considered as a smoldering form of ATLL because they do not have lymphoma or 5% or more of atypical cells in peripheral blood. These children represent pre-ATLL cases and are probably at a greater risk of developing ATLL. The pre-ATLL condition has been reported in 1.7% of asymptomatic adult carriers and 42% of them progressed to ATLL.
TREATMENT AND PREVENTION OF COMPLICATIONS

Because IDH is always associated with bacterial infection, treatment of IDH is currently aimed at controlling infection by *S aureus* and BHS. A treatment with sulfamethoxazole-trimethoprim (40 mg/kg/d of sulfamethoxazole and 8 mg/kg/d of trimethoprim) for 15 days and thereafter, one-half dose at night until the disease is controlled, has been recommended.\(^4^8,^5^1\) Erythromycin was used to treat one child who was allergic to sulfonamides and had an excellent response.\(^5^1\) Good results are being obtained in the Dermatologic Clinics of the Federal University of Bahia using cephalexin (50 mg/kg/d) for 10 days before the use of the sulfur drugs. Generally, the treatment lasts 3 to 12 months, depending on the response. If a relapse occurs during treatment, a complete dose must be restarted (Bittencourt AL, personal communication, 2013).

A combination of prophylactic immunoglobulin and perhaps antiretroviral therapy need to be investigated for possible use in the control of infection. Some investigators are also exploring the feasibility of an HTLV-1 vaccine.\(^7^5,^7^6\) It is recommended that these patients be carefully followed with clinical and laboratory examinations.

SUMMARY

As IDH may simulate other childhood cutaneous inflammatory conditions, it is imperative that the pediatricians know its characteristics so as to make a correct diagnosis and provide the correct treatment. These patients must be followed carefully even after disappearance of the cutaneous lesions so as to detect early possible adverse evolutions. Further research is necessary to determine factors that lead to only some infected children developing IDH, mechanisms behind the progression of IDH to HAM/TSP and ATLL, which in some parts of the world occurs very early. Considering that IDH and ATLL occur through vertical transmission of HTLV-1, it is important to prevent this route of transmission.

REFERENCES


73. Bittencourt AL, Oliveira MD, Argolo J, et al. Infective dermatitis associated with human-T-cell lymphotropic virus type-1 is a pre-ATL condition? In Annals of the 22nd European Academy of
Dermatology & Venereology Congress. Istanbul (Turkey), October 2–6, 2013.

