Adult T-cell leukemia/lymphoma

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Summary

Adult T-cell leukemia/lymphoma (ATL) is a malignancy of mature CD4+ T-cells caused by human T-cell lymphotropic virus type 1 (HTLV-1). Twenty million people are believed to be infected throughout the world, mostly in Japan, Africa, the Caribbean, and South America, particularly in Brazil and Peru. ATL affects about 5% of infected individuals and is classified in the following clinical forms: acute, lymphoma, primary cutaneous tumoral, chronic (favorable and unfavorable), and smoldering (leukemic and non-leukemic). Although it is considered an aggressive disease, there are cases with a long progression. We emphasize the importance of clinical classification as an indispensable element for evaluating prognosis and appropriate therapeutic approach. Since several cases have been published in Brazil and this disease is still poorly known, we decided to make a review paper for dissemination of clinical, hematological and pathological aspects, diagnosis, and therapy. The best way to reduce the occurrence of ATL would be halting the transmission of the virus through breastfeeding.

Keywords: human T-cell lymphotropic virus 1, adult T-cell leukemia/lymphoma, T-cell lymphoma, peripheral T-cell lymphoma, mycosis fungoides, cutaneous T-cell lymphoma.

Introduction

Adult T-cell leukemia/lymphoma (ATL) is a distinct neoplasia of peripheral T-lymphocytes caused by human T-cell lymphotropic virus type 1 (HTLV-1). It was described by Uchiyama et al. (1977),[1] in southwest Japan, when HTLV-1 had not yet been discovered, through observation of many patients with a different pattern of T-cell neoplasia.[1] These authors suspected a possible viral etiology.

HTLV-1 was discovered in 1980 after being isolated from cells derived from a cutaneous lymphoma, probably a mycosis fungoides (MF) lesion. Soon after, it was correlated to ATL.[2] In 1986 and in 1990, it was correlated to two other serious diseases, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[3] and infective dermatitis associated with HTLV-1 (IDH), respectively.[4] Although most infected patients remain asymptomatic, it is believed that in up to 10% of them the disease progresses during their lifetime.[5]

Several other inflammatory and autoimmune conditions, such as polymyositis, arthropathy, Sjögren's syndrome, and facial nerve paralysis have been associated with this virus.[6] Furthermore, infected individuals are more predisposed to developing infectious and parasitic diseases, and may also develop ophthalmic diseases, such as HTLV-1 uveitis.

HAM/TSP affects the central nervous system (CNS) and is characterized by progressive spastic paraplegia, sensory disorders of the lower limbs, neurogenic bladder, and bowel rhythm changes.[3] In Bahia, it occurs associated with ATL in 14% of cases.[7] IDH almost exclusively affects child/adolescent age ranges and is characterized by infected, intense, and recurrent eczema that mainly affects the scalp, face, and skin folds.[8] It has been noted that 37.5% of cases of ATL with cutaneous involvement described in Bahia have a history compatible with IDH. Furthermore, there are some well-documented cases of IDH associated with ATL.[9-13]

Epidemiology

The frequency of ATL varies according to the prevalence of HTLV-1 in different populations. It is estimated that

there are around 5 to 10 million infected individuals worldwide. It is most highly prevalent in Japan, Africa, the Caribbean Islands, and Central and South America, particularly Peru and Brazil.[14]

In Brazil, several regions are endemic for HTLV-1. A seroprevalence study of blood donors in the capitals showed a high prevalence of infection in São Luís (10.0/1,000), Salvador (9.4/1,000), Belém (9.1/1,000), and Recife (7.5/1,000). In Salvador, a study of a population sample identified the rate of carriers of the virus as 1.8%.[15]

The risk of carriers of the virus developing ATL during their lifetime is 6 to 7% in men and 2 to 3% in women, usually after a long latency period (20 to 30 years).[16] ATL corresponds to around 33% of the cases of cutaneous T-cell lymphoma at a reference service in Bahia,[17] and occurs predominantly in those of African descent.[7]

Although this disease is considered aggressive, cases with very long progression have been recorded.[18] ATL has been observed in children and adolescents, but not frequently.[18,19]

It is believed that the route of transmission responsible for the development of ATL is vertical, through breastfeeding,[20] although HTLV-1 may also be transmitted by blood transfusion, sharing of needles and unprotected sex. In Brazil, until November 1993 there were no mandatory serological tests on blood and organ donors, and to this day there is no standardization for prenatal HTLV-1 tests.[21,22]

Pathogenesis

ATL pathogenesis is not yet completely understood. The virus multiplies in the carrier through virological synapse and mitotic division. Through the synapses, various components of the virus, including its RNA, are transferred from the infected cell to an uninfected one. Inside the newly infected cell, the viral RNA is transcribed into DNA, becoming part of the human nuclear DNA, and giving rise to a newly infected clone. Using the second mechanism, the virus induces mitotic division of the infected cell, producing other identical infected cells with the proviral DNA inserted in the same site in the human genome, thereby increasing the number of cells of the infected clone. The expression of viral genes such as *tax* and *HBZ* stimulates the proliferation of infected lymphocytes and inhibits apoptosis. However, expression of the *tax* gene is not detected in infected cells originating from patients with ATL. In about 5% of HTLV-1 carriers, continuous and prolonged stimulation induces the accumulation of genetic and/or epigenetic alterations in infected cells, which acquire greater proliferative capacity, becoming established as the major clone and leading to ATL.[23,24]

Changes in the pattern of the cytotoxic immune response by both CD8 T-cells and natural killer (NK) cells from the innate immune response may lead to the development of the disease and may be conditioned by genetic factors. In this context, specific haplotypes of the human leukocyte antigen (HLA) and killer immunoglobulin-like receptors (KIR) genes may be associated with an abnormal immune response that could contribute to or slow down the progression of ATL, as already observed in HAM/TSP.[25] There is marked evidence that MHC class I genotyping influences the course of infection with HTLV-1.[26] For example, in a population from southern Japan, class I HLA-A2 and HLA-Cw8 alleles were considered as protective factors for the development of HAM/TSP, and were associated with a lower proviral load in asymptomatic carriers.[27,28]

Clinical characteristics

The natural history, clinical characteristics, and prognosis of ATL vary greatly, serving as the basis for the classification of the disease into five clinical types: smoldering, chronic, primary cutaneous tumoral (PCT), lymphoma, and acute. The smoldering type is subdivided into leukemic and non-leukemic, and the chronic type into favorable and unfavorable.[7,29,30] The acute, lymphoma, unfavorable chronic, and PCT types are considered aggressive, while the favorable chronic and non-leukemic smoldering types have a better prognosis.[7,29] There is still no data in the literature to assess the prognosis of the leukemic smoldering type.

In our case series, the median survival time (MST) of ATL is 4 months in the acute form, 9 in the lymphoma form, 21 in the PCT form, 18 in the chronic form, and 58 months in the smoldering form.[7]

The non-leukemic smoldering form without pulmonary involvement and the PCT are considered as primary cutaneous ATL.[31]

Less aggressive types may develop into more serious forms in up to 25% of cases, and this may be associated with specific changes in the gene expression profile.[32]

Table 1 presents the suggested conduct at the first consultation of a patient with suspected ATL and proposes in the medical history and physical examination the points that require more attention.

Characterizing the clinical form (Table 2) is fundamental because it will define the prognosis and therapeutic conduct.

TABLE 1 Conduct at the first consultation of a patient with suspected ATL.

Medical history	Supplementary examinations
History of the illness	**Laboratory**
Insidious/sudden onset	Serology confirmation for HTLV-1
Neurological symptoms	Complete blood count and blood smear ("flower" cells)
Digestive symptoms	Serum LDH
Performance status[70]	Serum calcium
Personal and family history	Serum albumin (a prognostic factor in the chronic form)
Birthplace	Urea (a prognostic factor in the chronic form)
IDH in childhood	Parasitology of the feces with the Baermann technique (to rule out strongyloidiasis)
HAM/TSP	Immunophenotyping and determination of soluble IL-2, if possible
ATL	**Imaging**
Dermatological diseases	CT scan of the neck, chest, abdomen and pelvis
Rheumatologic diseases	If this is not possible, carry out at least a chest x-ray and ultrasound of the abdomen and pelvis
Ophthalmic diseases	**Pathology**
Breastfed? For how long?	Skin, in the case of cutaneous lesions
Blood transfusion	Lymph node, in the case of lymph nodes with neoplastic features
Risky behavior	Myelogram and lumbar puncture in aggressive forms
Physical examination	**Useful in selected cases**
Attention to skin lesions	Pregnancy tests for women of childbearing age
Attention to auscultation of lungs	Endoscopy of the upper digestive tract for digestive symptoms
Attention to the palpation of lymph nodes, liver, and spleen	Skeletal examination in patients with the acute form and hypercalcemia
	PET scan, if available at the center
	CT scan, MRI, and/or lumbar puncture in all patients with acute and lymphomatous forms or in patients with neurologic manifestations not related to HAM/TSP

ATL: adult T-cell leukemia/lymphoma; IDH: infective dermatitis associated with HTLV-1; HAM/TSP: HTLV-1-associated myelopathy/tropical spastic paraparesis; LDH: lactic dehydrogenase; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging.

TABLE 2 Clinical classification of ATL (adapted from Shimoyama's classification).[7,29]

Clinical form	Lymphocytosis (> 4 x 109/L)	Atypical lymphocytes	LDH level	Hypercalcemia	Organs involved
Smoldering*	–	< 5% or ≥ 5%	≤ 1.5 x N	–	Skin and/or lungs only[¥]
PCT	–	...	≤ 1.5 x N	–	Cutaneous nodule/tumor lesions, mandatorily
Chronic **	+	≥ 5%	< 2 x N or ≥ 2 x N	–	Any organ except bone, GIT, and CNS
Lymphoma	–	≤ 1%	Variable	-/+	Lymph node, mandatorily, and/or any other organ
Acute	Usually +	Usually ≥ 5%	Usually ≥ 2 x N	+/-	Any organ and pleural effusions

*This form is divided into non-leukemic (< 5% atypical lymphocytes) and leukemic (≥ 5% atypical lymphocytes); **This form is divided into favorable and unfavorable, the latter being characterized by increased LDH (≥ 2 x N) and/or increased urea and/or decreased serum albumin; PCT: primary cutaneous tumoral; ... : not determined; LDH: serum lactic dehydrogenase; N: upper limit of the reference value; ¥skin and/or lung involvement may be lacking in the leukemic form; GIT: gastrointestinal tract; CNS: central nervous system.

Below is a list of the main characteristics of the various forms of ATL:

- **Smoldering form:** There is only involvement of the skin and/or lungs; however, involvement of these organs may be absent in the leukemic form. Lymphocytosis (≥ 4,000 cells/mL) and hypercalcemia are absent, with an increase in lactic dehydrogenase (LDH) up to 1.5 times the normal value and presence of up to 5% atypical lymphocytes in the peripheral blood. Cutaneous involvement may be identical to that in classic MF. In the leukemic variant, ≥ 5% atypical lymphocytes are observed.[29] However, in some reviews this subtype is not considered.[33,34]

- **Primary cutaneous tumoral (PCT):** The only differences in relation to the non-leukemic smoldering form are the presence of nodules or tumors on the skin and a worse prognosis.[7] In many studies, this type is included in the smoldering form.[35-37]
- **Chronic:** This is marked by lymphocytosis that may remain stable for months or years, an increase in LDH over 1.5 times the normal value, absence of hypercalcemia, with possible moderate lymphadenomegaly. There is an unfavorable subtype that is defined by low levels of serum albumin and high levels of serum LDH and/or urea, having a prognosis similar to the aggressive forms.[38] In the chronic form there is no involvement of the CNS, bone, gastrointestinal tract (GIT) or pleural effusions. There are often skin lesions, mainly in the form of disseminated papules.
- **Lymphoma:** This is characterized by marked lymphadenopathy without lymphocytosis and ≤ 1% abnormal lymphocytes in the peripheral blood. There may be increased serum LDH and serum calcium as well as involvement of the CNS, GIT and bones.[7,29] Histological proof of infiltration of T-cell lymphoma in the lymph nodes is required, associated with extranodal involvement or otherwise.
- **Acute**: This form displays high levels of lymphocytosis and atypical cells, including "flower" cells in the peripheral blood smear.[1,30] Any organ may be involved, including the CNS, GIT, and bone. Pleural effusions occur frequently.[39] Lytic bone lesions are frequent and may include up to 80% of cases.[40] A sharp increase in levels of serum LDH can also be noted. Lymphadenomegaly and cutaneous involvement are frequent. It should be taken into consideration that this form may present different aspects including, less commonly, the absence of lymphocytosis and hypercalcemia. In the absence of lymphocytosis, differential diagnosis against the lymphoma form depends on the presence of a high percentage of atypical lymphocytes in the peripheral blood.

ATL involves the skin in around 60% of cases and in all clinical forms, and is most frequent in the smoldering and chronic forms.[7] The lesions are multiple and generalized in around 50% of cases (Figure 1). Erythroderma, infiltrated plaques, papules, nodules, and tumors can be observed. Macular lesions are seen less frequently. Nodules and tumors are present in the aggressive forms (PCT, lymphoma, and acute forms). Erythroderma has been observed

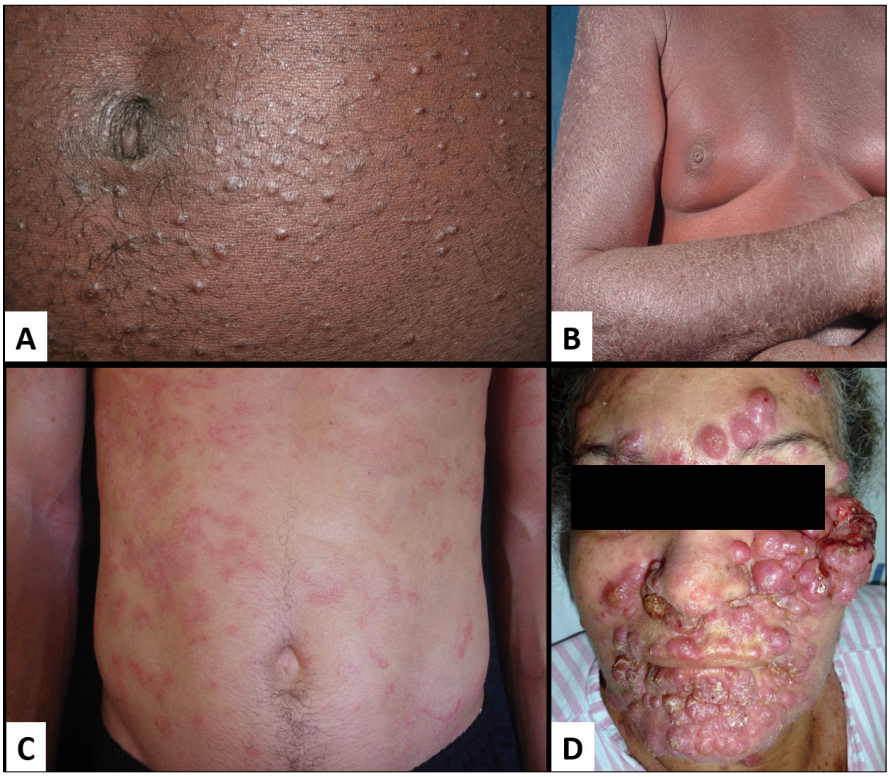

FIGURE 1 Examples of cutaneous lesions observed in ATL. A. Chronic form with papular pattern. B. Acute form showing exfoliative erythroderma. C. Smoldering form with a pattern of papules and erythematous scaly plaques. D. Primary cutaneous tumoral form.

in all clinical forms, with the exception of PCT, mimicking Sézary syndrome.[31] Although rare, vesicular lesions[41] and purpuric lesions[42] may also appear in ATL, similarly to that seen in MF. According to Sawada et al. (2011)[43] the skin lesions that correspond to cases with a worse prognosis are the erythroderma and nodular/tumor lesions. In their case series, all cases of erythroderma occurred in the acute form.

Diagnosis

Clinically, ATL diagnosis should be based on seropositivity for HTLV-1 associated with hematological and/or histopathological diagnoses of peripheral T-cell leukemia and/or lymphoma.[30]

Confirmation of infection with HTLV-1 is generally performed by enzyme-linked immunosorbent assay (ELISA), and should always be confirmed by Western blot and/or polymerase chain reaction (PCR).

Distinctive "flower" cells can be seen in peripheral blood smears, that is, medium and/or large lymphocytes with multi-lobed nuclei, densification of chromatin, and absent or small nucleoli. These are seen mostly in the acute and chronic forms (Figure 2A). These cells are considered pathognomonic of ATL and enable diagnosis alone.[44] Other atypical cells may have the following morphologies: chronic lymphocytic leukemia, lymphoblastic type, and pleomorphic with granular or vacuolar cytoplasm.[44]

Flow cytometry is an important test for the diagnosis of ATL. Most patients display a phenotype of mature CD4 cells. The following markers should be used: CD2, CD3, CD4, CD5, CD7, CD8, CD25, CD29, CD26, CD45RO, αβ T-cell, and HLA-DR receptors. Many cases of ATL do not express CD7 and CD26 and show decreased expression of CD3. The minimum markers required for this examination should include: CD3, CD4, CD7, CD8, CD25, and Ki-67.[30,31] This examination can also be performed on cerebrospinal fluid and pleural effusions.[45]

Patients with tissue infiltration should undergo a biopsy and pathological examination. Whenever possible, the ideal action is to investigate the type of viral integration in the peripheral blood mononuclear cells (PBMC) and/or fresh neoplastic tissue, which confirms the diagnosis of ATL if monoclonal.[30] The techniques used are the reverse and long-range PCR[46] and Southern blot.[47] Southern blot is mainly used when there is a greater amount of DNA (Figure 2B). These techniques are performed by few laboratories, and thus are not generally accessible. However, they are not essential to the diagnosis in most cases. Their importance is greater as scientific proof in cases with atypical aspects, such as those presenting very long progression. On the other hand, it is known that the occurrence of T-cell leukemia/lymphoma not associated with HTLV-1 is rare in patients infected with the virus.[30]

There are several differential diagnoses of ATL, including mature T-cell neoplasms such as MF, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma, and even Hodgkin's lymphoma.[7,48,49]

Anatomical-pathological aspects

In 120 cases observed in Bahia, the organs most affected by ATL were: the skin (66.7%), lymph nodes (56.7%), peripheral blood (53.3%), spleen (32.5%), bone marrow (27.5%), and liver (25%), although several other organs may be involved (data not published).

The histopathological patterns of ATL vary and mimic different types of T-cell lymphomas not associated with HTLV-1. However, in the World Health Organization's classification of cutaneous lymphomas,[50] all cases of leukemia/lymphoma associated with HTLV-1 are classified as ATL, regardless of the histological pattern and without taking into account that the pathologists can only diagnose this disease if they are aware of HTLV-1 infection. Without this information, the pathologist classifies these cases as PTCL-NOS, MF or, less often, ALCL.[51]

In cases with MF morphology, infiltration is by small and irregular cells, usually associated with epidermotropism, obliteration of the basal layer by atypical lymphocytes (Figure 3A) and Pautrier's abscesses. PTCL-NOS is characterized by moderate to marked pleomorphism (Figure 3B), and may also present epidermotropism of lymphocytes and Pautrier's abscesses. In the ALCL pattern, large, cohesive cells with abundant cytoplasm and anaplastic nuclei are noted.[31]

In ATL, the most commonly observed immunophenotype is CD2+/CD3+/CD4+/CD5+/CD7-/CD8-/CD20-/CD79a-/CD25+.[7] However, in 52 cases with cutaneous manifestation, 29% presented CD8+. It is important to include a macrophage marker in the immunophenotype, such as CD68, to differentiate the macrophages of large lymphocytes in cases with MF pattern.[17] In large-cell lymphomas, the CD30 and ALK markers are also important. The cases of ATL with ALCL pattern recorded in Bahia were CD30 and ALK-.[31] In addition, it is always important to determine the proliferative index of the ATL lesions, usually carried out using proliferation marker Ki-67 (Figure 3C). This evaluation is very important because there is a negative correlation between the proliferative index and the

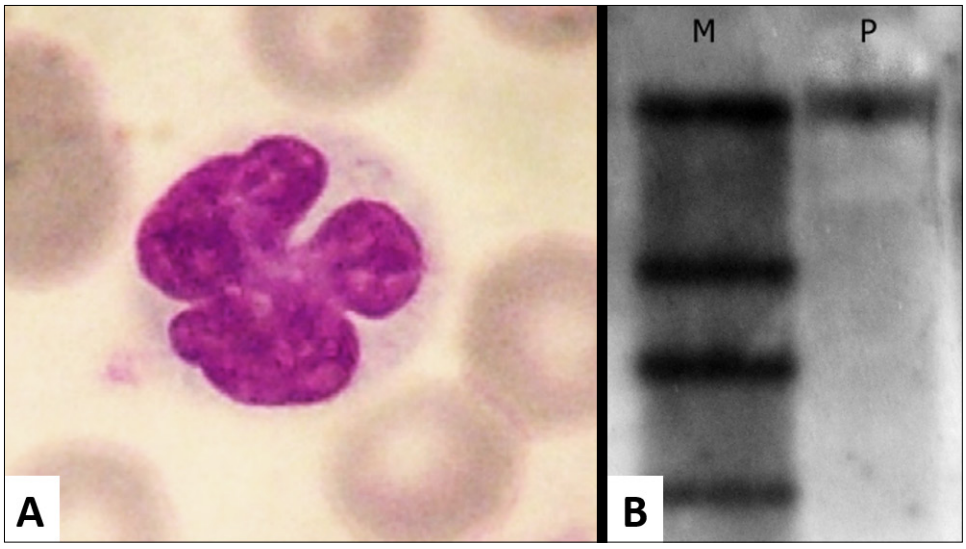

FIGURE 2 A. «Flower» cell on blood smear. B. Southern blot demonstrating monoclonal proviral integration. M: marker; P: patient.

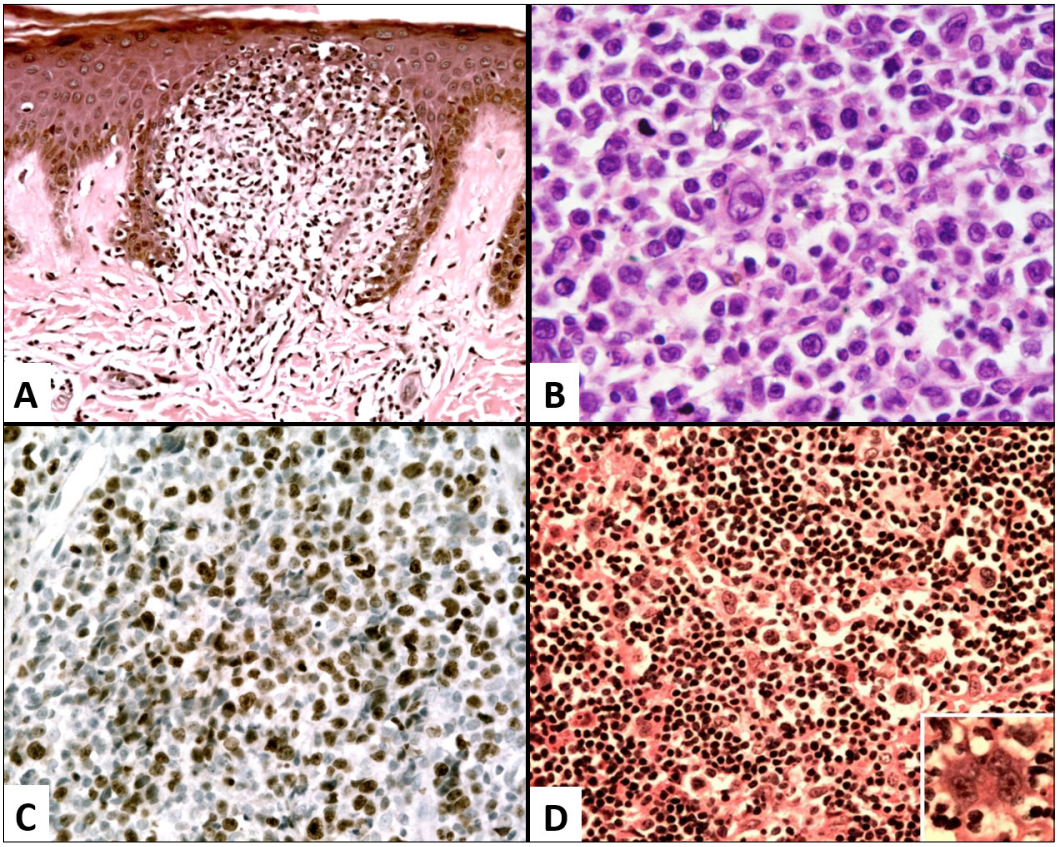

FIGURE 3 A. Skin biopsy of a patient with the chronic form and with a pattern of mycosis fungoides. Infiltration of small and medium lymphocytes in the superficial dermis, with pagetoid infiltration of the epidermis (HE, 100x). B. Skin biopsy of a patient with the primary tumor of skin form and with a pattern of peripheral T-cell lymphoma not otherwise specified. Note the accentuated cellular pleomorphism (HE, 500x). C. Biopsy of the same patient in figure B, showing a high proliferative index (Ki-67, 400x). D. Lymph node of chronic patient with a Hodgkin's lymphoma pattern. Reed-Sternberg and Hodgkin type cells seen amid a background of medium sized lymphocytes, with a T-cell phenotype (HE, 400x). A Reed-Sternberg cell highlighted in the lower right corner (HE, 560x).

MST.[7] In 60 to 70% of cases, the tumor cells express FoxP3 on the surface, which is a marker of regulatory T-cells.[52]

Confirming the stated above, a comparative study showed no significant difference between the histopathological aspects of PTCL-NOS and MF in individuals with and without infection with HTLV-1.[53]

Besides the aspects of PTCL-NOS and ALCL, a Hodgkin's type pattern may be observed in the lymph nodes, although infrequent, with a background of small and medium-sized T phenotype cells, with sparsely scattered Hodgkin and Reed-Sternberg type cells (Figure 3D). These cells are CD30, CD20, and/or CD15.[48,54] In our case series we found one case of Hodgkin type ATL among the 120 individuals studied. Rarely, ATL may be present in the lymph node presenting a pattern similar to angioimmunoblastic T-cell lymphoma.[48] It is important that pathologists consider Hodgkin-type ATL in the diagnosis of Hodgkin's disease.

As with cutaneous lymphomas in general, it is of paramount importance to differentiate between primary and secondary cutaneous ATL, as there is a statistically significant difference between them with respect to MST (48 months *vs.* 7 months).[31] In Bahia, among the cases of primary cutaneous T-cell lymphoma, 26.4% correspond to primary cutaneous ATL, while secondary ATL corresponds to 66.7%.[17] This data shows that ATL is frequent in Brazil.

Treatment

The treatment of ATL is based on the clinical type. Patients with aggressive forms, such as the acute, lymphoma or unfavorable chronic types, often receive chemotherapy. Recently, the Brazilian Ministry of Health published a guideline for ATL treatment including zidovudine (AZT) and interferon-α (IFN-α) as the first-line treatment for all clinical types, and associated chemotherapy only for lymphoma form.[55] In the United States and Europe, the association of AZT and IFN-α is the standard treatment for the leukemic forms. In Europe, chemotherapy alone is the first line treatment only for the lymphoma form of ATL, because survival with antiviral treatment alone is shorter.[56]

Traditionally, patients with the smoldering and favorable chronic forms are not submitted to specific treatments. In these forms, NB-UVB phototherapy is used for more superficial lesions and PUVA for more infiltrated lesions, with good results.[57,58] A recent study of patients with the smoldering form of ATL and cutaneous involvement demonstrated better survival in those treated with phototherapy combined with etoposide (25 to 75 mg/day for 2 to 4 weeks with a one-week interval or on alternate weeks).[35]

As such, the favorable chronic and smoldering types of ATL are considered less aggressive and should be kept under observation until possible progression of the disease, similar to management of chronic lymphocytic leukemia and smoldering myeloma. The treatment of the smoldering form with chemotherapy worsens the prognosis, which is similar to the unfavorable chronic form.[59]

Antiviral therapy using AZT and IFN was described in 1995[60] as an alternative treatment for ATL and has been used ever since. A meta-analysis with 254 patients recruited from four Western countries has been published, where all of the patients with the chronic and smoldering forms that were initially treated with AZT/IFN survived for more than 5 years. In acute patients treated initially with antivirals who had a complete response, survival at 5 years was 82%.[56] A summary of the recommendations of the 16th International Conference on HTLV-1 held in Montreal in June 2013 defined the combination of AZT and IFN as effective in the leukemic forms of ATL, which should be considered as the standard procedure and first-line therapy in this situation. In these cases, chemotherapy should only be started when a response to antivirals is not obtained.[61]

In relation to chemotherapy treatment, various combinations have been evaluated in Japan among ATL patients. However, MST ranged between 6 and 8.5 months.[62] The Japanese Clinical Oncology Group (JCOG) has conducted various clinical trials with several chemotherapeutic regimens. The best results for aggressive clinical forms (acute, lymphoma, and unfavorable chronic) were obtained with the VCAP-AMP-VECP regimen (vincristine, cyclophosphamide, doxorubicin, prednisone-doxorubicin, ranimustine, and prednisone-vindesine, etoposide, carboplatin, prednisone), which obtained a complete response rate of 40 *vs.* 25%, and an MST of 13 *vs.* 11 months, respectively, compared with the biweekly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen. However, due to the high toxicity of this regimen, especially in patients over 70 years old, CHOP regimens are preferred.[63] As some of these drugs are not available in the United States, hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone – methotrexate, cytarabine) is acceptable as an alternative regimen.[64] Due to frequent CNS impairment in aggressive forms (from 10 to 25%) intrathecal prophylaxis is recommended.[65]

Also in relation to the severe forms, it is worth mentioning that patients are immunocompromised and at high risk for fatal opportunistic infections, therefore prophylaxis for pneumocystis pneumonia and strongyloidiasis is recommended, among others, as well as screening for tuberculosis. Control measures must be adopted for calcium in addition to observing the possible development of tumor lysis syndrome.[66]

Autologous and allogeneic bone marrow transplantation (BMT) has been attempted in ATL in order to improve the outcome of these patients. Autologous BMT does not seem to have many benefits due to frequent relapses and the occurrence of infections.[67] Several researchers refer to an improvement in survival with allogeneic BMT, especially using myeloablative regimens. However, a high mortality rate has limited its use.[68] Studies using a reduced intensity conditioning regimen show an interesting and even curative option in approximately 15% of cases, probably due to a graft *versus* tumor effect.[68] In a retrospective analysis of 386 patients in Japan treated with allogeneic BMT under any induction regimen, survival at 3 years was 33%. Four factors were associated with having a poor prognosis: being older than 50 years, being male, disease without complete remission at the time of BMT, and having an unrelated donor.[69]

Many new agents for ATL are under study with promising results in the treatment of ATL, for example, anti-CCR4 monoclonal antibody (mogamulizumabe), IL-2 fusion inhibitor (denileukin diftitox), histone deacetylase inhibitors (HDAC), purine nucleoside phosphorylase inhibitor (forodesine), proteasome inhibitor (bortezomib), etc.[68]

Prognosis

A study of 854 patients using a multivariate analysis determined the indicators of a poor prognosis as being: high performance status,[70] high levels of LDH, being aged > 40 years, more than three areas involved and hypercalcemia.[71] Most of these indicators are present in the acute form, which has the worst prognosis.[30] In relation to the chronic form of the disease, as mentioned above, patients who have high levels of LDH and urea and low levels of albumin have the worst prognosis.[38] A recent multicenter retrospective study with 807 patients newly diagnosed with the acute and lymphoma forms of ATL identified Ann Arbor clinical staging, performance status and three continuous variables (age, serum albumin, and dosage of the soluble IL-2 receptor) as independent prognostic factors.[72]

In a study in Bahia that included 70 cases of ATL assessed using a univariate analysis, the factors related to poor prognosis were: the acute, lymphoma and PCT clinical forms, a proliferative index higher than 18%, presence of large cells in the histology, and the absence of cutaneous lesions. However, cutaneous involvement predominated in the forms with a better prognosis, and was present in all cases of the smoldering form and in 90% of cases of the chronic form.[7]

Prevention

For the prevention of ATL it is also important to halt vertical transmission of the HTLV-1, with infected mothers recommended not to breastfeed and being provided with formula and suitable pediatric assistance to children, as is already the case with HIV-infected mothers.[22,73]

Given that strongyloidiasis predisposes the development of ATL due to clonal expansion of lymphocytes, and considering that this form of parasitosis may be asymptomatic, frequent investigations for such in asymptomatic carriers of HTLV-1 are important, having in mind that proper treatment of this parasitosis can reverse clonal expansion.[74] Atypical cells, including "flower" cells, can be found in 10 to 43% of asymptomatic carriers of HTLV-1, and thus they are considered as being at high risk of developing ATL.[75] These patients should be monitored at regular intervals in order to detect the early development of ATL.

Conclusion

1. Clinical classification of ATL is fundamental to determining the prognosis and therapeutic conduct.
2. ATL can simulate other T-cell lymphomas not clinically and histologically associated with the virus, such as MF, PTCL-NOS, and ALCL.
3. Serology for HTLV-1 should be performed in all patients with a diagnosis of mature T-cells leukemia/lymphoma, so that cases of ATL receive adequate orientation.
4. Although new therapeutic options are gradually improving the prognosis of ATL patients, treatment continues to be a major challenge. New studies and measures will be necessary in order to optimize therapeutic combinations.
5. It is important for the Brazilian Ministry of Health to consider the inclusion of HTLV-1 serology in prenatal programs to decrease the incidence of ATL.

Resumo

Leucemia/linfoma de células T do adulto

A leucemia/linfoma de células T do adulto (LLcTA) é uma neoplasia de células T maduras CD4+ causada pelo vírus linfotrópico para células T humanas tipo 1 (HTLV-1). Acredita-se que existem cerca de 20 milhões de pessoas infectadas em todo o mundo, principalmente no Japão, na África, no Caribe e na América do Sul, particularmente no Brasil e no Peru. A LLcTA acomete cerca de 5% dos indivíduos infectados e classifica-se nas seguintes formas clínicas: aguda, linfomatosa, tumoral primária de pele, crônica (favorável e desfavorável) e indolente (leucêmica

e não leucêmica). Embora seja considerada uma doença agressiva, há casos com longa evolução. Salientamos a importância da classificação clínica como elemento imprescindível para avaliação do prognóstico e conduta terapêutica adequada. Como já foram publicados vários casos no Brasil e essa doença ainda é pouco conhecida, decidimos fazer um trabalho de revisão para divulgar os seus aspectos clínicos, hematológicos, anatomopatológicos, diagnósticos e terapêuticos. O melhor meio de reduzir a ocorrência de LLcTA seria sustando a transmissão vertical do vírus pela amamentação.

Palavras-chave: vírus 1 linfotrópico T humano, leucemia-linfoma de células T do adulto, linfoma de células T, linfoma de células T periférico, micose fungoide, linfoma cutâneo de células T.

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