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Review article

Neoplastic hematological diseases associated with HTLV-1 infection

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ABSTRACT

Adult cell lymphoma/leukemia (ATLL) is a type of lymphoma consisting of T-cells that are related to infection with the human T lymphotropic virus (HTLV-1). Four clinical forms have been described (leukemic, lymphomatous, chronic, smoldering) and the phenotype corresponds to regulatory CD4+ T cells. The histological characteristics are variable, with neoplastic cells showing a size ranging from small to large and atypical nuclei with irregular contours. A series of genetic and molecular alterations have been described, which partially explain the lymphomagenesis of the neoplasm, some of which are also factors related to the clinical course and overall survival. ATLL is a neoplasm with a poor prognosis, but in recent years new targeted therapies have been designed, with encouraging responses. This neoplasm should continue to be studied to improve treatment and evolution.

Introduction

Adult T-cell lymphoma/leukemia (ATLL) is a type of mature T-cell lymphoma associated with human T lymphotropic virus 1 (HTLV-1) infection. It occurs exclusively in adults and has a geographical distribution. Four clinical forms have been described (leukemic, lymphomatous, chronic, smoldering) and, recently, a cutaneous form. The phenotype corresponds to regulatory CD4+ T cell (Treg). A series of complex structural chromosomal alterations and non-specific mutations have been recognized some of them associated with T-cell receptor signaling, prognosis and with the design of targeted therapies. In general, ATLL is a neoplasm with a poor prognosis.[1,2]

Epidemiology

The distribution of the disease depends on the geographical distribution of HTLV-1.[1] HTLV-1 affects 15–20 million people worldwide, but it is endemic in certain regions, as South Western of Japan, Caribbean countries, South America countries (principally Colombia, Ecuador, Peru), equatorial Africa, Melanesia, and in small groups in the Middle East.[3,4] The HTLV-1 prevalence increases gradually with age, especially among women in all highly endemic areas. The estimates range of HTLV-1 infected individuals is 5–10 million, although a correct estimate in other highly populated regions, such as China, India, the Maghreb, and East Africa, has not been considered, therefore, the current number of HTLV-1 carriers could be much higher.[3,5] Antibodies to HTLV-1 are found in 6–37% of healthy adults aged over 40 in endemic areas in Japan and are increasing in non endemic areas in Japan and the United States, suggesting spread by move of carriers.[4] The incidence in Japan is 2.5% among carriers of HTLV-1.[6] The period of latency of the disease is long, being the people affected infected by the virus from very early in life. Up to 5% of HTLV-1 carriers will develop ATLL, usually after a latency of two to four decades following infection early in life. Overall lifetime risk of progression to ATLL is 2.1% in women and 6.6% in men.[7] The age range of presentation of the disease is from the third to the ninth decade of life with an average age of 58 years. It is more frequent in men, with male-to-female ratio of 1.5: 1.[1] The modes of HTLV-1 transmission are mother to child, sexual transmission, and transmission with contaminated blood products.[8–10] Differences in the frequency of the various clinical forms have been observed in the relationship with the geographic region. For example, the lymphomatous form is more common in the Western Hemisphere than the acute form.[1,2]

Etiology

HTLV-1 is a single-stranded RNA virus with a diploid genome, which infects human $CD4^+$ helper T cells, undergoes reverse transcription to proviral DNA.[11] Lymphomagenesis in HTLV-1 infection is a multiple-step process. The pattern of HTLV-1 integration is distinct in every infected cell (randomly integrates into the host genome), except in cells that are clonally related.[12] Over time, the high abundance of a

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clone of cells with a single viral integration site constitutes "monoclonality," correlating with neoplasia.[11] Patients with incipient ATLL or those with early-stage disease may contain T-cell clones with defective or partial viral integration.[13] Early in infection, HTLV-1 is spread via cell-to-cell conjugation, viral budding, and the formation of an extracellular viral assembly, which can easily transmit to adjacent immune cells.[14] HTLV-1 enters cells mainly through cell-to-cell contact via three cellular molecules: heparan sulfate proteoglycan, neuropilin 1, and the glucose transporter GLUT1. Neuropilin 1 appears to function as the viral receptor.[15] The provirus itself encodes products, which promote cellular transformation, including the retroviral long terminal repeats gag, pol, env, and a pX region at the 3′ end. The latter encodes the regulatory proteins a 40-kDa cell-transforming oncoprotein Tax, REX, and human basic zipper factor HBZ, which are implicated in proliferation.[1,2,11]

The TAX protein is a transcriptional activator of the viral long-terminal repeat and can act by transactivation to deregulate a variety of cellular genes, leading to activation of signal transduction, deregulation of the cell cycle, and induction of genetic instability resulting in multiple cytogenetic abnormalities.[16–19]

TAX active the nuclear factor-κB (NF-κB), the cAMP response element binding transcription factor (CREB)/ATF family (leucine zipper protein), and AP-1 families. TAX also binds to proteins that inhibit NF-κB. TAX upregulates the expression of both IL-2 and IL-15. IL-15 uses the beta and gamma chains of IL-2R for signaling. TAX also upregulates IL-15Rα in ATLL cells.[20] In addition, TAX can inactivate p53,[21] and inhibits CDKN2A, promoting continuous cellular proliferation of HTLV-1 infected T-cells.[22] IL-6 also may be activated by TAX which may cause hypercalcemia. Activation of NF-κB also appears to play a role in the production of osteoclast-activating factors.[23] On the other hand, HZB enhances TGF-β signaling, supports proliferation of ATLL cells through suppression of C/EBPα signaling[24] suppresses apoptosis by attenuating the function of FoxO3a, and dysregulates the Wnt pathways to support proliferation and migration of ATLL cells.[25] Aberrant CpG methylation also appears to influence tumorigenesis.[26] The constitutive activation of JAK/STAT signal transduction pathways in HTLV-1 associated ATLL has led to the use of JAK2 kinase inhibitors in some clinical trials of ATLL.[12]

Both TAX and HZB proteins are often silenced in both HTLV-1 carriers and ATLL patients, allowing infected cells to evade the host response by interactions with the host microenvironment or by other epigenetic mechanisms.[27–29]

Clinical features

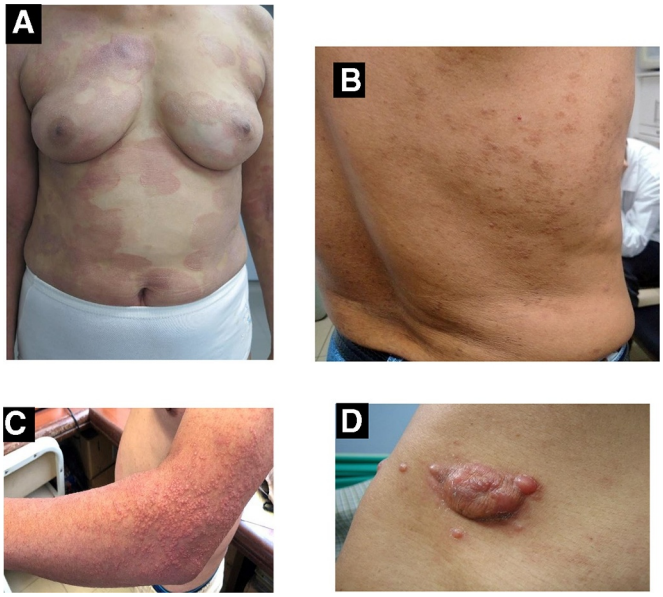
The classification of Shimoyama[1,2,30,31] recognizes four clinical forms:

A Acute: it corresponds to 60% of the cases and is characterized by lymphadenopathy, visceromegaly, involvement of other extranodal sites (central nervous system, bone, pleural effusion, ascites, gastrointestinal tract), presence of neoplastic cells in peripheral blood (flowers cells), hypercalcemia, and elevated lactate dehydrogenase (LDH).

B Lymphoma: it corresponds to 20% of the cases. The extension of the disease is like the previous one but without neoplastic cells in peripheral blood. There is also hypercalcemia and elevated LDH.

C Chronic: it corresponds to 15% of the cases. This clinical form is characterized by lymphadenopathy and neoplastic infiltration in skin, spleen, liver and lung. Occasionally, neoplastic cells are observed in peripheral blood. Hypercalcemia is not found, and the LDH elevation is less than double its normal value.

D Smoldering: it corresponds to 5% of the cases. The neoplastic compromise is restricted to the skin and lung. Neoplastic cells can be found in peripheral blood in up to 5% of cases. In this clinical form, hypercalcemia is not observed and the LDH elevation is discrete (less than 1.5 of its normal value).



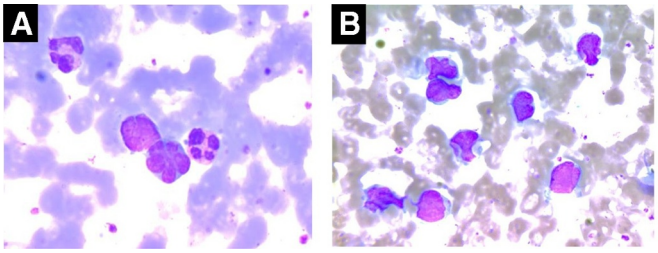
Figs. 1. Various forms of skin lesion in ATLL: erythematous (A), papular (B, C), and nodular (D). Courtesy: Dr. Francisco Bravo.

Acute and lymphoma clinical forms have a median survival of less than 1 year and a projected 4-year survival of only 5%. The clinical course is less aggressive in patients with chronic or smoldering disease, but median survival is also less than 5 years.

Usually there are leukocytosis and eosinophilia and the bone marrow may be hypercellular, with myeloid hyperplasia. Patients with ATLL are immunosuppressed, which facilitates opportunistic infections (cytomegalovirus, herpes zoster, Pneumocystis jiroveci and Strongyloides stercoralis). The compromise sites in ATLL are: skin, in more than 50% of the cases (Fig. 1A-D), gastrointestinal tract, lungs, liver, central nervous system (CNS), and bone marrow.[1,2]

The classification of Shimoyama is based on circulating cell counts, involvement organs, and DHL levels, however, sometimes there are difficulties in classifying some cases. For example, the acute subtype with bulky lymphadenopathy may behave more clinically like the lymphoma subtype, and the smoldering subtype with only circulating abnormal lymphocytes may overlap with a non-malignant HTLV-1 carrier state.[30] In the lymphoma type, the risk of progression can be predicted according to DHL, blood urea nitrogen, and albumin levels.[31,32] Factors that may predict poor prognosis in acute ATLL include poor performance status, elevated LDH level, at least four total involved lesions, hypercalcemia, age greater than 40 years, thrombocytopenia, eosinophilia, bone marrow involvement, high interleukin-5 serum level, CCR4 expression, and presence of lung resistance-related protein, TP53 mutation, and/or CDNK2A gene deletion. Levels of IL-2 receptors are also an independent prognostic factor.[31,33] Approximately 10–20% of patients with aggressive ATLL will have CNS progression.[31] Prognostic factors of predictive value for chronic ATLL include high LDH, low albumin, and high blood urea nitrogen levels, deletion of the CDKN2A gene, and molecular alterations.[2,34] HLA class has recently been reported as a novel prognostic factor in ATLL.[35]

Recently a new primary cutaneous variant of adult T-cell lymphoma (PTC-ATL) with poor prognosis has been proposed.[36] In a Japanese retrospective study of ATLL with cutaneous lesions, 5-year survival rate was 0% in nodule, tumoral and erythrodermic types compared with more than 40% in other types (exfoliative rash, erythema, papules).[37,38] PCT-ATL is distinct, with cutaneous lesions appearing as tumors that grow rapidly and whose histology shows large, atypical cells with a high proliferative index and scant epidermotropism.[37–39]



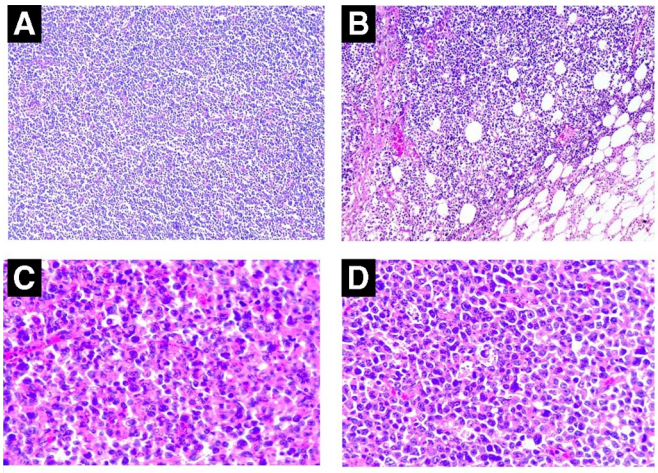
Figs. 2. Peripheral blood of patient with ATLL, showing flower cells with hyperlobulated nuclei with clumped, and hyperchromatic chromatin (A). Other cells show less lobulated nuclei.

Regarding image studies, in patients with hypercalcemia, they may show lytic bone lesions. FOG-PET/CT is usually positive in sites of disease activity. Thoracic CT studies can show enlarged lymph nodes and various lung and airway abnormalities, such as ground-glass attenuation and bronchial wall thickening, particularly those with aggressive ATL. Bronchiectasis is usually similarly found in patients with indolent ATL and aggressive ATL.[40]

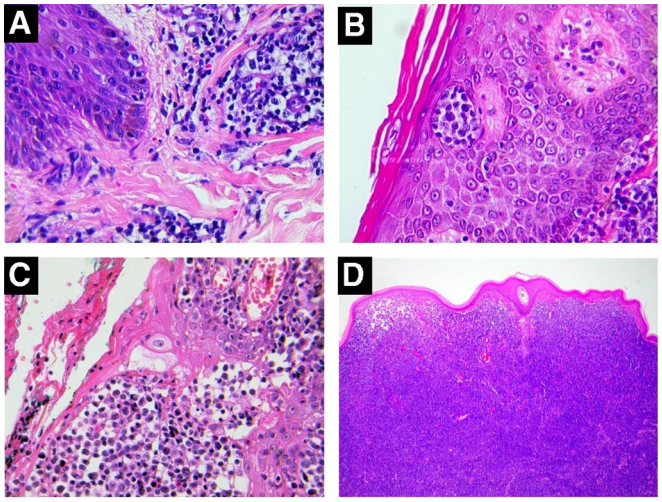
Histopathology

The cytological characteristics are nonspecific and varied; however, there are some frequent findings. The neoplastic cells in the peripheral blood are markedly polylobated and have been termed flower cells (Fig. 2A and B). Conversely, the nuclear irregularities in Sézary cells are much subtler. The nuclear chromatin is coarsely clumped, hyperchromatic, with distinct, sometimes prominent, nucleoli, although the flower cells usually do not manifest prominent nucleoli. The cytoplasm is basophilic, and cytoplasmic vacuoles may be seen.[1,2,41,42]

Histologically, lymph node affected show diffuse effacement of the normal architecture by tumor cells infiltration (Fig. 3A-D). The cytologic composition of the neoplastic infiltrate is very diverse. The atypical lymphoid cells are medium to large sized with pronounced nuclear pleomorphism, irregular nuclei, chromatin clumping and prominent nucleoli. Blast-like cells with transformed nuclei could be present in variable proportions. Giant cells with convoluted or cerebriform nuclear contours may be present. Rare cases may be composed predominantly of anaplastic-like tumor cells. Small Flower cells can be seen, mixed with large transformed cells. Large transformed cells have vesicular nuclei and usually multiple eosinophilic or basophilic nucleoli. The last ones may be relatively uniform in size, with round to oval nuclear contours. The inflammatory background is usually sparse,



Figs. 3. Lymph node diffusely infiltrated by ATLL. The morphology is varied, showing small neoplastic cells (A, B), or medium to large cells, with moderate pleomorphism (C). In some cases, a starry sky pattern can be observed (D).

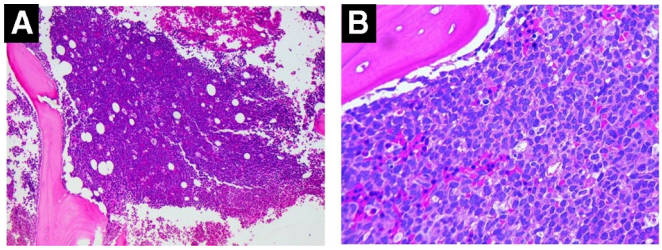


Figs. 4. Skin biopsies showing infiltration by ATLL. Invasion of the dermis can be observed with mild epidermotropism in initial lesions (A), with Pautrier microabscesses in more advanced lesions, focal (B) or disseminated (C), or with severe invasion of the dermis in nodular lesions (D).

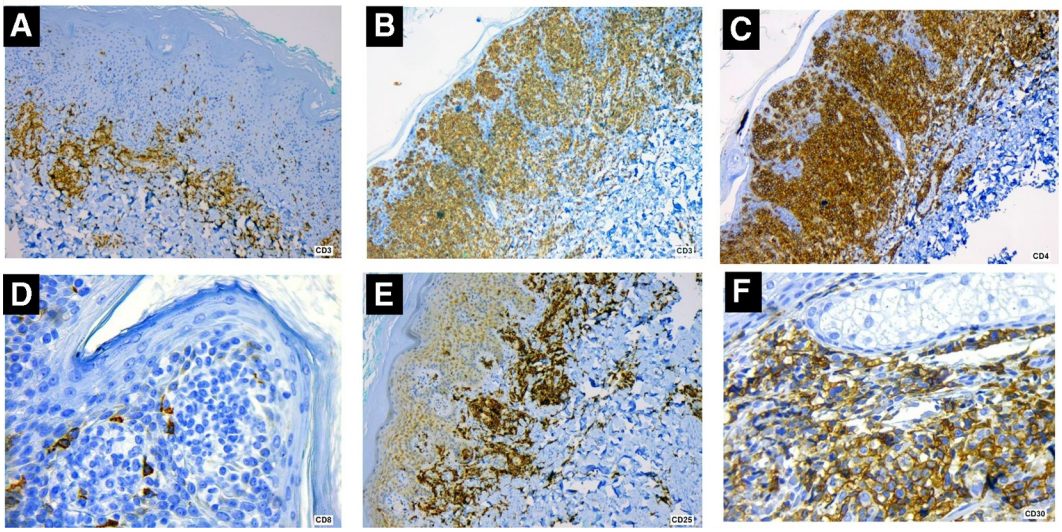
with scanty eosinophils. In an incipient phase of adult T-cell lymphoma/leukemia, such as the smoldering type, lymph nodes may exhibit a Hodgkin lymphoma-like histology, associated with less aggressive disease. In these cases, lymph nodes are infiltrated by small to medium-sized cells with irregular contours, mixed with Reed-Sternberg-like, CD30 and CD15 positive cells. These cells are Epstein-Barr virus-positive B lymphocytes.[1,2,43]

More than 50% of patients with ATLL show skin lesions. In the skin, architectural patterns are described as perivascular, nodular, or diffuse. The lichenoid and interstitial patterns are rare.[44] The cutaneous neoplastic infiltrate is variable, and, in some cases, it can resemble inflammatory lesions (Fig. 4A-D). Usually, epidermotropism with Pautrier-like microabscesses is observed, but in contrast to Sézary's syndrome or mycosis fungoides, the neoplastic infiltrate is usually monomorphic and relatively confluent, without numerous histiocytes or eosinophils. Dermal infiltration is mainly perivascular, but larger tumor nodules with extension to subcutaneous fat may be observed. Perineural invasion and annexotropism can also be observed, including follicular mucinosis.[1,2,11,44]

Bone lesions show involvement of the marrow by ATLL and show bone destruction (Fig. 5A and B). Some patients can have lytic bone lesions as a result of prominent osteoclastic resorption without tumor involvement. Bone marrow involvement is not prominent and may contain patchy atypical lymphoid infiltrates.[2,45] The neoplastic cells in the chronic and smoldering variants of the disease usually show minimal cytologic atypia.[2]



Figs. 5. Bone marrow infiltrated in the leukemic form of ATLL. In this case, the pattern of infiltration is diffuse (A), with medium to large cells showing hyperchromatic nuclei with irregular contours (B).



Figs. 6. ATLL infiltrating skin, showing a typical profile of immunoexpression, with positivity for CD3, CD4 and CD25 (A, B, C, E) and negativity for CD8 (D) in neoplastic cells. In this case, CD30 expression is also observed (F).

Immunophenotype

The tumor cells are usually strongly positive for CD2, CD3, CD5, CD4 and CD25, but negative for CD7, CD8 and cytotoxic molecules, including TIA-1, Granzyme B and perforin (Fig. 6A-F). Few cases are CD4-negative and CD8-positive or double-positive for CD4 and CD8. Some cases show large transformed neoplastic cells positive for CD30, which may also have anaplastic characteristics.[1,2,43,44] The CD30 expression is a target of antibody therapy (brentuximab vedotin).[2] The CD4− positive alpha-beta T cells also express the alpha chain of the interleukin-2 receptor (IL-2R).[46] Recently, a prognostic index (PI) for chronic- and smoldering-type ATL identified soluble interleukin-2 receptor (sIL-2R) levels as an independent prognostic factor.[47] CD52 is also usually positive, which has therapeutic implications for the treatment with anti-CD52 humanized antibody (alemtuzumab [Campath]). The CC chemokine receptor 4 (CCR4) is also often expressed and is associated with skin involvement and poor outcome. It allows the use of anti-CCR4 antibody (mogamulizumab) as effective treatment.[32,48] The expression of both CD25 and FOXP3 suggest that ATLL cells may be the equivalent of regulatory T (Treg) cells.[49,50] 68% of the cases are positive for FOXP3 in at least some of the neoplastic cells, although usually only a small minority (Fig. 7).[51]

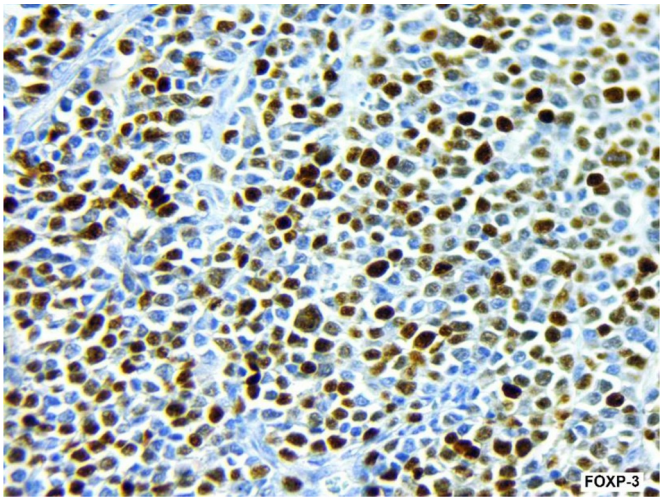


Fig. 7. FOXP3 nuclear expression in a case of lymphomatous ATLL.

Genetic and molecular features

TCR genes are clonally rearranged. HTLV-1 is clonally integrated to neoplastic T-cells in patients with ATLL. As mentioned before, the viral proteins Tax and HBZ play a crucial role in the development and progression of ATLL, as well as genetic and epigenetic aberrations. Higher frequencies of TP53 and IRF4 mutations and several copy number alterations, including PD-L1 amplifications and CDKN2A deletions, are more predominant in aggressive than indolent diseases. In the other hand, STAT3 mutations are more frequent in indolent ATLL. Moreover, several genetic alterations, such as PD-L1 amplification, can predict the clinical outcomes independent of other prognostic factors.[1,2,52]

Some alterations have been described more frequently in the acute form than in the lymphomatous form: losses of CDKN2A/p16 INK4a, CDKN2B/ARF p14, and CD58. In contrast, there are other more frequent alterations in the lymphomatous form, such as Gain of RXRA. This alteration and the loss of ITGB1, CCDC7, or CD68, are associated with progression to the acute form.[11]

Other alterations described in ATLL are loss of heterozygosity (LOH) and downregulation of miR-145. The latter may be associated with worsened survival in patients with aggressive-type ATLL.[53]

A study an integrated genomic and transcriptomic analysis of > 400 ATLL cases showed considerable genomic instability, with a high number of structural variations per case. The most frequently mutated genes were *PLCG1, PRKCB, VAV1, IRF4, FYN, CARD11*, and *STAT3*. There were also CCR4 and CCR7 mutations, and other mutations affect the NF-κB pathway and genes involved in T-cell signaling. CCR4 mutations are hypothesized to alter the migration of ATLL cells as well as enhance AKT activation with ligand engagement. Whole-genome sequencing identified intragenic deletions involving *TP73*. Recurrent splice-site mutations were found in *GATA3, HNRNPA281*, and *FAS*.[54–56] Other genes over expressed including *LYN, CSPG2* and *LMO2*.[45]

ATLL cells show numerous complex structural cytogenetic abnormalities, most frequently in chromosome 6. It has been described deletions, with breakpoints at bands q11, q13, q16q23, q21q23, q22q24, and q23q24, findings associated with aggressive clinical course.[57,58] Approximately 10% of cases have translocations that involve T-cell receptor-αΔ gene locus on 14q11.[59] Overexpression of *BIRC5* (survivin) a gene that blocks apoptosis and may play a role in resistance of ATLL to chemotherapy, has also been described.[60] *CCR4* mutations are associated with gain of function and increased Pl3K signaling.[61]

Recently some research has been reported indicating that there are

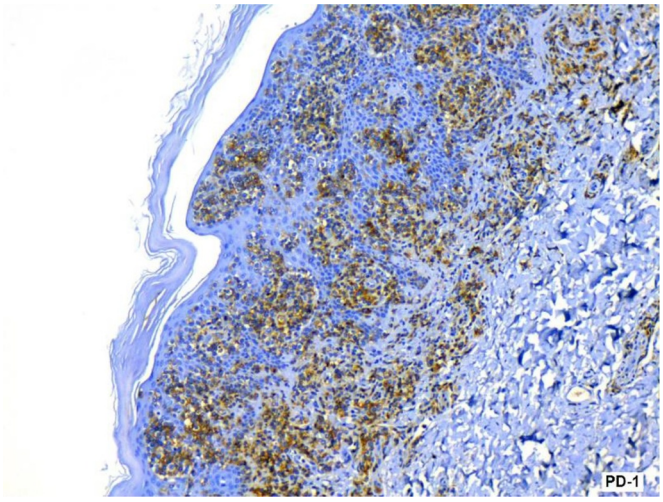


Fig. 8. ATLL infiltrating skin, showing expression of PD-1.

differences genetic and molecular alterations between the cases of ATLL from Western countries and those from Japan. In a study, the authors performed targeted exon sequencing on 30 North American ATLL patients and compared the results with the Japanese ATLL cases. Although the frequency of TP53 mutations was comparable, the mutation frequency in epigenetic and histone modifying genes was significantly higher, whereas the mutation frequency in JAK/STAT and T-cell receptor/NF-κB pathway genes was significantly lower. The most common type of epigenetic mutation was that affecting EP300. Authors conclude that North American ATLL has a distinct genomic landscape that is characterized by frequent epigenetic mutations that are targetable preclinically with DNA methyltransferase inhibitors.[62] Another study with Caribbean patients, showed cytogenetic features like Japanese ATLL, but certain significant variations in frequency of specific chromosomal abnormalities were observed. For example, in Japanese patients the most frequent numerical changes in chromosomes were trisomy 3, while the Caribbean cohort showed high frequency of copy number loss in chromosome 14. The most common recurrent chromosomal rearrangement breakpoints in the Japanese patients was 14q32, while in the Caribbean cohort was 6q21. Another difference was the higher frequency of high complex karyotype (>10 aberrations) in Caribbean cases, which was associated with significant shorter survival. The authors commented that some factors might have contributed to the observed cytogenetic differences between Caribbean and Japanese ATLL patients, for example, the clinical presentation was aggressive in the Caribbean cases, while in the Japanese cases, indolent cases were included.[63] In a series of cases from Peru, USA, Brazil, and Spain, there were several recurrent copy number variations (CNVs) that have not been previously demonstrated in ATLL: homozygous deletion of the T-cell receptor alpha chain constant region (TRAC; 14q11.2) was see in most samples demonstrating the importance of T-cell related pathways in ATLL. Another recurrent CNV in that cohort involved the ETS1 and FLI1 proto-oncogenes (11q24.3).[64]

Prognosis

In addition to those already molecular factors mentioned, other factors with probable negative prognostic impact have been identified, such as PD-1 in patients with cutaneous lesions (Fig. 8).[65] Aggressive types of ATLL (acute and lymphomatous) have an overall survival with a range from 2 weeks to more than 1 year. Although smoldering and chronic forms are indolent and not very symptomatic, 25% of cases can progress to aggressive forms.[66]

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