HEMATOLOGIC MANIFESTATIONS OF HTLV1 INFECTION

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1

- It is estimated that the human T lymphotropic virus type 1 (HTLV-1) infects approximately 20 million people worldwide.
- Associated diseases, however, manifest only in 5–10% of infected individuals.

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- The onset of the disease usually occurs 20–30 years after viral infection and is primarily associated with vertical transmission, mainly through breastfeeding by a seropositive woman.

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- Markers of HTLV-1 infection (infection status, antibody titer, and provirus load) are associated with hematologic and biochemical alterations, such as:
- Lymphocyte abnormalities(atypical, cleaved, and reactive lymphocytes),
- Anemia (inversely correlated with MCV),
- Decreased eosinophils,
- Elevated lactate dehydrogenase levels.

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- HTLV-1 has been reported in association with other blood diseases, such as:
- Acute myeloid leukemia,
- Idiopathic thrombocytopenic purpura,
- Myelodysplastic syndrome.

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- There is some evidence that HTLV-1 is a causative agent of cutaneous T-cell lymphoma.

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Adult T-cell leukemia/lymphoma (ATLL)

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- Adult T-cell leukemia/lymphoma (ATLL) is a mature, peripheral T-cell neoplasm caused by human T-cell leukemia virus type 1 (HTLV-1).

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- HTLV-1 establishes lifelong latency in human T cells.
- Malignant transformation leading to ATLL occurs in HTLV-1–infected individuals with a cumulative lifetime risk of 4% to 7%.
- Incidence is less than 5% in HTLV-1-infected people.

9

- HTLV-1 is an oncogenic retrovirus that preferentially infects CD4 T-cells.
- Although HTLV-1 is primarily found in CD4+ T cells, other cell types in the peripheral blood of infected individuals have been found to contain HTLV-1, including CD8+ T cells, dendritic cells and B cells.

10

- The cancer is thought to be due to the pro-oncogenic effect of viral RNA incorporated into host lymphocyte DNA.
- Chronic stimulation of the lymphocytes at the cytokine level may play a role in the development of the malignancy.

11

- ATLL occurs predominantly in adults between the sixth and seventh decades.
- ATL occurs more commonly in adults at least 20 to 30 years after the onset of HTLV-1 infection and is more common in males, and individuals infected in childhood may be at a higher risk of developing ATL.

12

- The time between infection and onset of cancer also varies geographically.
- It is believed to be about sixty years in Japan and less than forty years in the Caribbean.

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- ATLL is classified into 4 clinical subtypes, namely as defined by Shimoyama criteria:
- Acute,
- Lymphomatous,
- Chronic,
- Smoldering.

14

Adult T-cell leukemia/lymphoma subtypes and diagnosis criteria

Parameter[a]	Criterion for ATL subtype			
	Smoldering	Chronic	Lymphoma	Acute
Lymphocyte count (10^9 lymphocytes/liter)	Less than 4	4 or more[d]	Less than 4	More than 4
% atypical lymphocytes	5 or more	5 or more	1 or less	More than 5
LDH level	1.5× normal upper limit	2× normal upper limit	—[b]	—[b]
Calcium level (mmol/liter)	Less than 2.74	less than 2.74	—[b]	More than 2.74[b]
Presence of:				
Lymphadenopathy	No	No	Atypical lymphocyte in histological analysis	—[b]
Skin lesions	—[c]	—[b]	—[b]	—[b]
Pulmonary lesions	—[c]	—[b]	—[b]	—[b]
Liver lesions	No	—[b]	—[b]	—[b]
Spleen lesions	No	—[b]	—[b]	—[b]
CNS lesions	No	No	—[b]	—[b]
Bone lesions	No	No	—[b]	—[b]
Ascites	No	No	—[b]	—[b]
Pleural effusion	No	No	—[b]	—[b]
Gastrointestinal tract lesions	No	No	—[b]	—[b]

[a] See reference 89.

[b] Not essential.

[c] Not essential; cases of atypical lymphocytes are fewer than 5%; other items have to be completed, and histological analysis of a lesion has to confirm malignancy.

[d] Lymphocytosis, T-cell count of 3.5×10^9 cells/liter or more.

15

- The most aggressive acute and lymphomatous forms are by far the most common, and patients frequently present with lymphadenopathy, hepatomegaly, splenomegaly, hypercalcemia, and involvement of the skin, lung, bones, and other organs.

16

- The lymphomatous type often presents with extensive lymphadenopathy and a relative absence of ATLL cells in the peripheral blood (<1%).
- The acute type usually presents with leukemia and high levels of serum lactose dehydrogenase (LDH).

17

- The smoldering and chronic forms present with $<4 \times 10^9$ or $\geq 4 \times 10^9$ lymphocytes/L in the peripheral blood, respectively; normal or elevated LDH (<1.5 or 1.5-2 times the upper normal value, respectively); involvement of lung, skin, or liver (in chronic only), but no other extranodal sites; and no hypercalcemia.

18

- In the smoldering or chronic form,the skin alterations are predominant, with papulae, plaques, tumor, or long-time erythroderma .

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- The diagnosis of ATLL requires the detection of ATLL cells in peripheral blood of patients with the acute, chronic, or smoldering type with leukemic manifestations.

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- Typical ATLL cells have convoluted nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm.
- These cells are called flower cells and are considered characteristic of ATLL .

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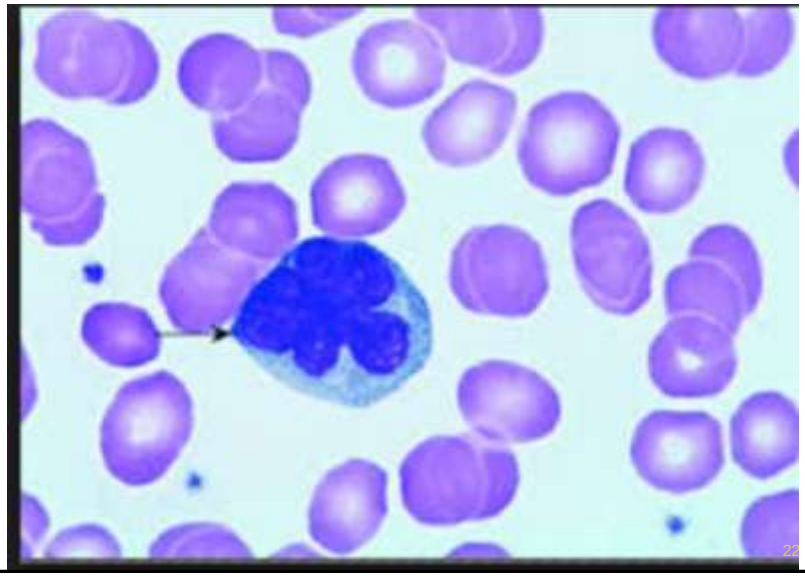

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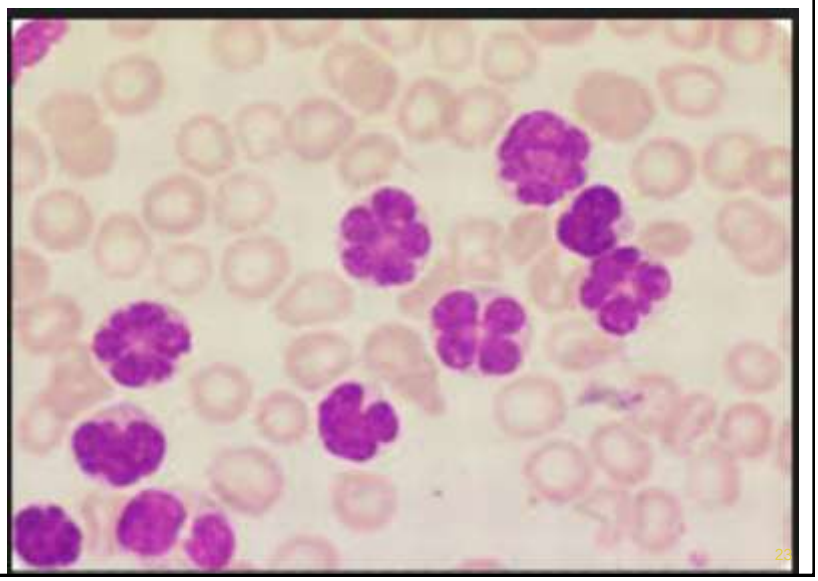

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- Analysis of CD3, CD4, CD7, CD8, and CD25 is required for an immunophenotypic diagnosis.

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- Comorbid opportunistic infections are often seen in ATLL patients as a result of immunosuppression caused by dysfunctional HTLV-1–infected T cells.
- Parasitic infections, especially strongyloidiasis, and fungal infections are frequently associated with all forms of ATLL.

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- The diagnostic criteria for ATLL include the detection of antibodies against HTLV-1 in the peripheral blood of a patient with T-cell lymphoma or leukemia, the presence of hypercalcemia, and, in cases of tumor, monoclonal insertion of HTLV-1 proviral DNA into the tumor cells.
- Skin lesions, high leukocyte counts, and $CD25^{+}$ cells may be present or absent.

26

- When the diagnosis of ATLL is not done by peripheral blood examination or when a new lesion appears during the monitoring of indolent ATLL, biopsy of suspicious lesions should be considered.
- Frequently involved tissues include lymph nodes, skin, liver, spleen, lung, gastrointestinal tract, bone marrow, bone, and CNS.

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- AZT-IFN is now considered a first-line treatment option for nonlymphomatous ATLL and is recommended under National Comprehensive Cancer Network treatment guidelines.
- Despite this, the long-term prognosis of ATLL remains poor.

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- The rate of survival varies depending on the subtype: 4 to 6 months for the acute type, 9 to 10 months for the lymphomatous type, 17 to 24 months for the chronic type, and 34 months to more than 5 years for the smoldering type.

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- Only allogeneic hematopoietic stem cell transplantation (allo-HSCT) appeared to be curative, with a 4-year OS of 26% in 227 patients and an MS of 5.9 months, in part due to disease relapse or transplant-related mortality.

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- The major prognostic factors are advanced performance status, high calcium or lactic dehydrogenase (LDH) levels, age of more than 40 years, and more than three involved lesions.
- Bone marrow involvement is an independent poor prognostic factor for ATLL.

31

- HTLV-1-seropositive individuals should be advised not to donate blood, semen, organs, or milk, where milk banks are available.
- Prevention of mother-to-child transmission would probably have the most significant impact on the occurrence of HTLV-1 infection and associated diseases.

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- Avoidance of breastfeeding is fundamental, since it is the major form of vertical transmission of HTLV-1.
- In the case of pregnancy, a cesarean section should be recommended, to minimize the risk of perinatal transmission.

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- Recommendations to prevent sexually transmitted infections should be emphasized, including condom use and avoiding multiple and unknown sexual partners and paying or receiving money for sex.
- When one of the partners in a stable relationship is negative, the need for condom use should be emphasized.

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- Counseling and education of intravenous drug users (IDU) to implement harm reduction practices may be effective in preventing HTLV-1 infection in this population group.

35