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Adult T-cell leukemia/lymphoma: Unusual immunophenotype by flow cytometry

Editor,

Adult T-cell leukemia/lymphoma (ATLL) is a unique T-cell neoplasm etiologically linked to human T-lymphotropic virus type 1 (HTLV 1). It usually affects adults and has poor prognosis with median survival time of 13 months even if multiagent chemotherapy is given. The immunophenotype of ATLL is that of activated mature T lymphocytes express CD2 and CD5 and are usually CD4+/CD8–. CD3 and T-cell receptor (TCR) αβ may be downregulated and CD7 is negative. The strong expression of alpha chain of the interleukin-2 receptor recognized by monoclonal antibody CD25 is a distinctive feature.[1]

A 56-year-old male patient presented with extensive maculopapular skin lesions and tiredness. On investigation, the white blood cell count was 225,000/mm^3. Platelet count was 80,000/mm^3. Lactate dehydrogenase (LDH) was 3159 (normal range 313–618 μ/L). Serum calcium level was increased 18.3 (normal range 8.4–10.2 mg/dL). Peripheral blood examination showed 88% atypical cells with scant to moderate amount of cytoplasm, irregular/multilobated nuclei [Figure 1]. Bone marrow aspiration and biopsy showed atypical lymphoid cells with irregular nuclei infiltrating marrow. Flow cytometric evaluation of peripheral blood showed the atypical cell population to be CD2+, CD3+, CD4–, CD5–, CD7–, CD8–, CD25+, CD56–, CD34–, Tdt–, CD64–, TCR αβ+, and TCR γδ– [Figure 2]. Correlating clinical feature (extensive skin lesions), biochemical parameters (elevated calcium and LDH), cell morphology (cells with irregular/lobated nuclei), and immunoprofile (CD2+, CD3+, CD7–, CD25+, TCR αβ+ Tdt– and CD34–), the diagnosis of ATLL was made even though the CD4–, CD8–, CD5 – immunophenotype is rare in ATLL. Serum HTLV 1 estimation, done by Western blot method, was positive.

ATLL, a peripheral T-cell lymphoma associated with HTLV 1 infection, is an aggressive neoplasm characterized by poor response to chemotherapy and short survival. Because of the diverse clinical features, ATLL is classified into acute, chronic, lymphomatous and smoldering types.[1]

ATLL is endemic in southwestern Japan, the Caribbean basin and parts of central Africa. The distribution of ATLL is related to the prevalence of HTLV infection. The diagnosis of ATLL is by positive serology study for anti-HTLV 1 antibody and confirmation by Southern blotting. There are only limited case reports of ATLL from India. The largest series describes 15 cases of serum HTLV 1 positive ATLL from Kerala, South India.[2]

T-cells arise from bone marrow precursors which undergo maturation and differentiation in the thymus. The cortical thymocytes have an immature T-cell phenotype and express Tdt, CD1a, CD5, CD7, and cytoplasmic CD3. Medullary T-cells express CD2, surface CD3 and CD7 and are negative for Tdt and CD1a. The immature cortical thymocytes are CD4– and CD8–. Maturing thymocytes coexpress CD4 and CD8. More mature T-cells express either CD4 or CD8.[1]

ATLL is associated with HTLV 1 which usually infects CD3+, CD4+, CD25+, HLADR + mature T-cells. A majority of the

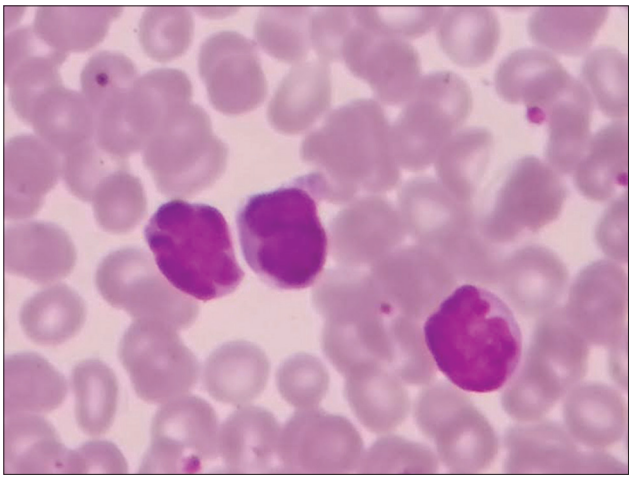

Figure 1: Peripheral smear showing atypical cells with irregular nuclei (Giemsa, ×1000)

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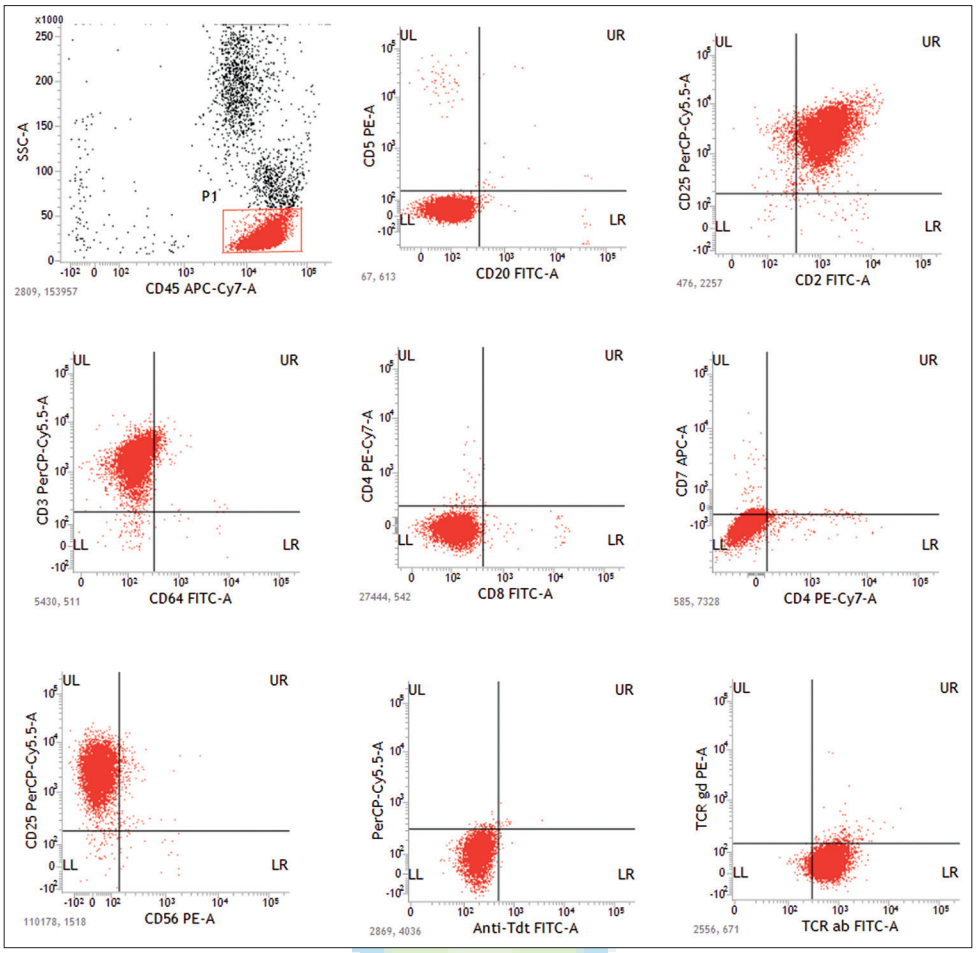

Figure 2: The gated populations of cells are positive for CD2, CD3, CD25, T-cell receptor αβ and are negative for CD4, CD5, CD7, CD8, CD20, Tdt, CD56, CD64, T-cell receptor γδ

cases of ATLL are associated with mature CD4+, CD8– T cell phenotype. A few cases of CD4+, CD8+ and CD4–, CD8+ ATLL have been reported. Double negativity (CD4–, CD8–), as in the present case, is exceptionally rare.[3,4] The expression of CD3 and lack of Tdt rules out an immature T-cell phenotype in these double negative cases. ATLL that lack CD2, CD3 or CD5 have been reported which are associated with worse prognosis.[3]

HTLV 1 infection is restricted to T-cells *in vivo*. Although HTLV 1 infects both CD4+ and CD8+ T-cells, the leukemogenic potential is restricted to CD4+ T-cells. Leukemic transformation of CD4– T-cells induced by HTLV 1 is not been fully characterized.

CD4+ T-cells act via cytokine production. Regulatory T-cell (Treg) is a CD4+ T-cell which functions to shut off and suppress immune responses. Tregs express CD25 and transcription factor FOXP3. The marked immunosuppression in ATLL can be explained by the immunosuppressive action of Treg.[1]

There are two types of T-cells depending on the TCR αβ T-cells and TCR γδ T-cells. The majority is TCR αβ T cells and is CD4+ and CD8+ whereas TCR γδ T-cells comprise <5% of all normal T-cells and are CD4– and CD8– and usually lack CD5. A very rare subset of CD4– and CD8– TCR αβ T-cells has been described in the peripheral blood and in the skin, the function of which is not known.[5] In our case, the atypical cells were CD5–, CD4–, CD8–, and TCR αβ+.

Diminished surface expression of the TCR αβ/CD3 complex is a specific feature of ATLL cells. Suzushima *et al.* noted that surface expression of TCR αβ/CD3 complex was diminished in double negative (CD4–, CD8–) ATLL cells, in a pattern similar to the CD4+ ATLL cells, despite the lack of CD4 or CD8 as the coreceptor.[6] They concluded that TCR αβ-positive T-cells with or without CD4 are the sole target of HTLV 1-induced leukemia.

Although the atypical lymphocytes in ATLL have a typical immunoprofile (express CD2, CD3, CD4, CD5, and CD25, rarely express CD8 and lack CD7), atypical immunophenotypes have been described rarely such as CD4–/CD8+, CD4+/CD8+, CD4–/CD8–, CD2–, CD3–, and CD5–.[4,7] The awareness of the atypical immunophenotype will help avoid diagnostic dilemma, especially in nonendemic areas.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Oshima K, Jaffe ES, Kikuchi M. Adult T cell leukemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, PA: IARC; 2008. p. 281-4.
2. Nair RA, Jacob PM, Nair SG, Prem S, Jayasudha AV, Sindhu NP, *et al*. Adult T cell leukemia/lymphoma in Kerala, South India: Are we staring at the tip of the iceberg? J Hematop 2013;6:135-44.
3. Kumura T, Hino M, Yamane T, Ohta K, Nakao T, Wakasa K, *et al*. Triple-negative (CD3-/CD4-/CD8-) adult T cell leukemia/lymphoma, histologically presenting as CD30 (Ki-1)-positive anaplastic large cell lymphoma with clonal Epstein-Barr virus genome. Leukemia 2001;15:994-5.
4. Lin TH, Wu HC, Hsieh YC, Tseng CE, Ichinohasama R, Chuang SS. CD4 and CD8 double-negative adult T-cell leukemia/lymphoma with monomorphic cells expressing CD99: A diagnostic challenge in a country non-endemic for human T-cell leukemia virus. Pathol Int 2013;63:132-7.
5. Groh V, Fabbi M, Hochstenbach F, Maziarz RT, Strominger JL. Double-negative (CD4-CD8-) lymphocytes bearing T-cell receptor alpha and beta chains in normal human skin. Proc Natl Acad Sci U S A 1989;86:5059-63.
6. Suzushima H, Asou N, Hattori T, Takatsuki K. Adult T-cell leukemia derived from S100 beta positive double-negative (CD4- CD8-) T cells. Leuk Lymphoma 1994;13:257-62.
7. Dahmoush L, Hijazi Y, Barnes E, Stetler-Stevenson M, Abati A. Adult T-cell leukemia/lymphoma: A cytopathologic, immunocytochemical, and flow cytometric study. Cancer 2002;96:110-6.

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