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Commentary

Jejune and Sophomoric-T Cell Prolymphocytic Leukaemia

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T cell prolymphocytic leukaemia (T PLL) is an aggressive T cell leukaemia comprised of miniature to intermediate mature T lymphocytes. The leukaemia exhibits elevated quantifiable white blood cells (WBCs) with significant cellular dissemination and incrimination of diverse organs.

Generally, accompanying lymphocytosis exhibits CD4+ and T cell leukaemia/lymphoma protein1 (TCL1) immuno-phenotype. Fluorescent *in situ* hybridization (FISH) can be beneficially employed to assess genetic rearrangements within T cell leukaemia/lymphoma protein1 (TCL1).

Additionally designated as T cell chronic lymphocytic leukaemia or small cell variant of T cell prolymphocytic leukaemia, obtaining appropriate therapeutic outcomes may be challenging and the disorder is accompanied by inferior prognostic outcomes.

The exceptional T cell prolymphocytic leukaemia configures ~2% of mature lymphocytic leukaemia. Commonly, elderly population or adults > 30 years are implicated with median age of disease emergence at 65 years [1,2].

Neoplastic lymphocytes of T cell prolymphocytic leukaemia disseminate within peripheral blood, bone marrow, regional or distant lymph nodes, spleen, hepatic parenchyma or various cutaneous surfaces.

T cell prolymphocytic leukaemia is associated with an amalgamated overexpression of T cell leukaemia/lymphoma protein1 (TCL1) family of proteins with consequent activation of AKT/protein kinase B induced cellular proliferation along with functional deficit of ATM protein [1,2].

Of obscure aetiology, enhanced possible emergence of T cell prolymphocytic leukaemia occurs with ataxia-telangiectasia delineating germline mutations of ATM gene.

T cell prolymphocytic leukaemia delineates a significant tumour burden along with elevated white blood cell count with median quantification of 50 x 10^9/Litre to 60 x 10^9/Litre [1,2].

Comprehensive incrimination of bone marrow (100%), mono-cellular, bi-cellular or pancytopenia, hepatosplenomegaly, regional or disseminated lymph node enlargement, lesions confined to mucosa and cutaneous surfaces along with implication of diverse organs with visceral dysfunction is encountered. Constitutional symptoms are prominent.

An estimated ~30% subjects represent with inactive disease wherein disease progression into active disease occurs within one to two years.

Cogent criterion indicative of disease progression are manifested as ~lymphocyte doubling time (LDT) of < 6 months or amplified lymphocyte count > 50% within 2 months [1,2].

Peripheral blood examination exhibits lymphocytosis as discerned with miniature to intermediate lymphocytes incorporated with cytoplasmic projections, clumped nuclear chromatin and prominent, variable centric nucleolus.

Small cell variant of T cell prolymphocytic lymphoma is encountered in an estimated ~25% instances and is constituted of miniature neoplastic lymphocytes devoid of prominent nucleoli.

Cerebriform variant of T cell prolymphocytic leukaemia configures ~ 5% of T cell prolymphocytic leukaemia [1,2].

T cell prolymphocytic leukaemia represents with perivascular and diffuse infiltration of uniform, miniature to intermediate neoplastic lymphocytes within diverse tissues. Incrimination of spleen is accompanied by neoplastic dissemination within red pulp [1,2].

T cell prolymphocytic leukaemia is immune reactive to CD2, CD3, CD5, CD7, CD52, T cell alpha/beta (TCRαβ) or T cell leukaemia/ lymphoma protein1 (TCL1). Generally, neoplastic cells demonstrate CD4+/CD8- immuno-phenotype.

T cell prolymphocytic leukaemia is immune non reactive to terminal deoxynucleotidyl transferase (TdT), CD1a, CD16 or CD30 [3,4].

Upon flow cytometry, mature CD3+T lymphocytes enunciate pan T markers as CD2, CD5 and CD7 along with immune reactive CD52. Majority (~60%) of neoplastic lymphocytes manifest CD4+/CD8- immuno-phenotype. Besides, CD4+/CD8+ or CD4-/CD8+ immuno-phenotype may be encountered.

T cell prolymphocytic leukaemia manifests clonal T cell receptor genetic rearrangements as encountered with T cell receptor beta/ T cell receptor gamma (TRB/TRG) genetic loci.

Fluorescent *in situ* hybridization (FISH) may be beneficially employed for detecting rearrangement of T cell receptor locus within T cell leukaemia/lymphoma protein1 (TCL1) family of genes [3,4].

Besides, genetic rearrangements within T cell leukaemia/lymphoma protein1A (TCL1A) and T cell leukaemia/ lymphoma protein1B (TCL1B) are comprised predominantly of inv(14)(q11;q32) and t(14;14)(q11;q32). Also, MTCP1 genetic rearrangement t(X;14)(q28;q11) is exceptionally discerned.

T cell prolymphocytic leukaemia is infrequently devoid of TCL1A/TCL1B or MTCP1 genomic rearrangements.

Majority (~80%) of T cell prolymphocytic leukaemia demonstrate a complex karyotype with chromosomal anomalies within chromosomes 6, 8, 12p, 17p and genetic mutations within ATM gene situated upon chromosome 11q23. Additionally, genomic mutations or alterations within TP53 and genes of JAK/STAT pathway as IL2RG, JAK1, JAK3 or STAT5B may be encountered.

T cell prolymphocytic leukaemia requires segregation from neoplasms such as Sézary syndrome, adult T cell leukaemia/lymphoma (ATLL), T lymphoblastic leukaemia/lymphoma (T ALL) or T cell large granular lymphocytic leukaemia (T LGLL) [3,4].

T cell prolymphocytic leukaemia can be appropriately discerned with cellular morphology as demonstrated with peripheral blood examination and flow cytometry.

Morphological assessment of bone marrow biopsy or surgical tissue samples from diverse solid organs as lymph node, spleen, cutaneous surface or hepatic parenchyma in association with precise immuno-phenotyping with immunohistochemistry or flow cytometry is optimally recommended.

A variable cellular countenance is observed with fluorescent *in situ* hybridization (FISH). However, the manoeuver remains superfluous in instances delineating overexpression of TCL1 within neoplastic T cells as discerned with immunohistochemistry or flow cytometry [3,4].

T cell prolymphocytic leukaemia is appropriately categorized with consensus criteria established by T cell prolymphocytic leukaemia International Study Group. Comprehensive determination of major criteria or initial two major criterion in combination with a singular minor criterion appear confirmatory of T cell prolymphocytic leukaemia.

Major criteria are designated as:

- 5 x 10^9/litre cells of T cell prolymphocytic leukaemia as discerned within peripheral blood or bone marrow
- Monoclonal T cells as detected by molecular methodologies or flow cytometry
- Anomalous chromosome 14q32 or chromosome Xq28 OR aberrant expression of T cell leukaemia/lymphoma protein1A (TCL1A), T cell leukaemia/lymphoma protein1A (TCL1B) or MTCP1 gene.

Minor criteria are designated as:

- Anomalies within chromosome 11 (11q22.3) or ATM gene
- Anomalies within chromosome 8, idic(8)(p11), t(8;8) or trisomy 8q
- Anomalies within chromosome 5, 12, 13, 22 or complex karyotype
- Neoplastic incrimination within specific sites as spleen or visceral effusions [3,4].

T cell prolymphocytic leukaemia demonstrates elevated peripheral blood lymphocytes with lymphocytosis > 100 x 10^9/ litre, elevated serum lactate dehydrogenase (LDH) and beta2 (β-2) micro-globulin.

Human T lymphotropic virus 1 (HTLV1) appears indiscernible upon serological assay.

Significant hepatosplenomegaly along with regional and distant lymph node enlargement is encountered [3,4].

Positron emission computerized tomography (PET/CT) exhibits moderate to elevated forced expiratory volume (FEV).

Active T cell prolymphocytic leukaemia necessitates precise therapeutic intervention. Standardized chemotherapeutic regimen are comprised of alemtuzumab, an anti-CD52 molecule. Besides, allogeneic bone marrow transplantation may be variably and beneficially employed.

Adoption of chemotherapeutic agents as BCL2, JAK3 or histone deacetylase (HDAC) inhibitors are experimental and require extended evaluation [3,4].

Generally, T cell prolymphocytic leukaemia is associated with an overall inferior prognostic outcome with median survival of active disease of up to 2 years.

Factors contributing to adverse prognostic outcomes emerge as

- Pleural effusion
- Elevated serum lactate dehydrogenase (LDH) > 1668 International Units/Litre
- Decimated haemoglobin (< 9.3 grams/decilitre)
- Complex karyotype [3,4].

Major criterion
>5 × 10^9/L cells of T-PLL phenotype within peripheral blood or bone marrow
Clonal T cells with PCR for TRB/TRG or flow cytometry
Chromosomal anomaly of 14q32 or Xq28 OR expressed TCL1A/B or MTCP1
Minor criterion (minimally one required)
Anomalies of chromosome 11(11q22.3; ATM)
Anomalies of chromosome 8; idic(8)(p11), t(8;8), trisomy 8q
Anomalies of chromosome 5,12, 13,22 or complex karyotype
Involvement of T-PLL specific site (splenomegaly, effusions)

Table 1: *Diagnostic criterion of T cell prolymphocytic leukaemia [5].*

T-PLL: T Cell Prolymphocytic Leukaemia; PCR: Polymerase Chain Reaction; TRB/TRG: T Cell Receptor Beta/ T Cell Receptor Gamma Loci; TCL1: T Cell Leukaemia/Lymphoma Protein1.

T-PLL	cyTCL1$^+$, CD3$^+$, CD4$^+$, CD5$^+$, CD7$^+$, CD8$^+$, CD4$^+$/ CD8$^+$
T-ALL	TdT+, CD1a+
Leukemic PTCL	cyTCL1-
T cell large granular lymphocytic leukaemia	CD8+, CD57+, CD16+
Sézary syndrome	CD7-, CD4+, CD25+
Adult T cell lymphocytic leukaemia	CD4+, CD25+, HTLV1+

Table 2: *Immuno-phenotype of differential diagnosis of T cell prolymphocytic leukaemia [5].*

T-PLL: T Cell Prolymphocytic Leukaemia; T-ALL: T Cell Acute Lymphoblastic Leukaemia; PTCL: Peripheral T Cell Lymphoma; TdT: Terminal Deoxynucleotidyl Transferase; HTLV1: Human T Lymphotropic Virus1.

Disease related constitutional symptoms	Significant fatigue ECOG ≥, B symptoms as pyrexia, night sweats, > 10% loss of body weight in ≤ 6 months.
Symptomatic bone marrow failure	Haemoglobin < 10 g/dL, platelets < 100 x 10^9/L
Rapidly enlarging lymph nodes, spleen and liver	> 50% in 2 months, diameter doubling < 6 months, symptomatic enlarged lymph node, spleen and liver
Increasing lymphocytosis	If > 30 x 10^9/L, > 50% in 2 months, lymphocyte doubling time < 6 months
Extra-nodal involvement	Organ infiltration, pleural or peritoneal effusion, central nervous system involvement

Table 3: *Criterion for staging and therapy with T cell prolymphocytic leukaemia [5].*

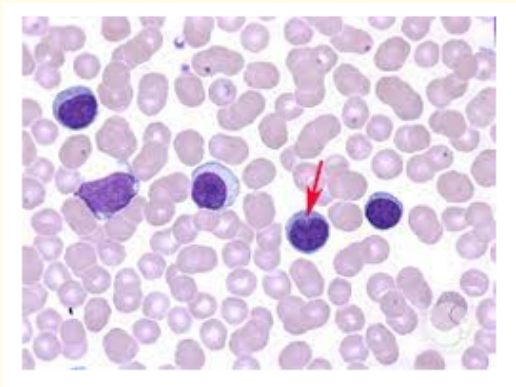

Figure 1: *T cell prolymphocytic leukaemia demonstrating circulating small to medium lymphocytes with minimal cytoplasm, clumped nuclear chromatin and conspicuous nucleoli [6].*

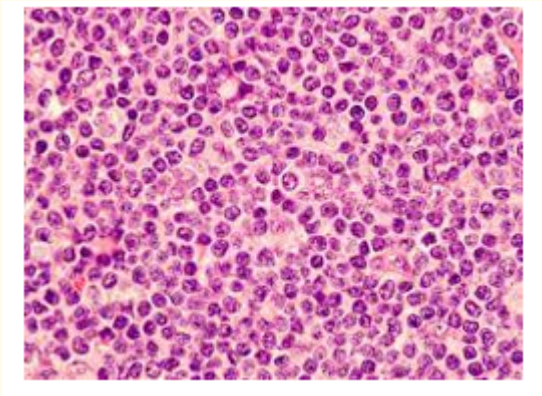

Figure 2: *T cell prolymphocytic leukaemia exhibiting diffuse dissemination of small to intermediate neoplastic lymphocytes with scant cytoplasm, clumped nuclear chromatin and prominent nucleoli [7].*

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6. Image 1 Courtesy: ASH.com

7. Image 2 Courtesy: Pathology outlines.

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