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The Populous Smidgen-T Cell Large Granular Lymphocytic Leukaemia

Editorial

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Editorial

T cell large granular lymphocytic leukaemia is a chronic, T cell lymphoproliferative disorder which characteristically demonstrates a clonal proliferation of mature, cytotoxic T cells. Additionally designated as T cell large granular lymphocytosis or T cell lymphoproliferative disease of granular lymphocytes, T cell large granular lymphocytic leukaemia is associated with diverse autoimmune disorders. Generally, neoplastic CD8+ T lymphocytes appear immune reactive to NK cell immune markers. An estimated (50%) subjects manifest a STAT3 / STAT5b genetic mutation. Of obscure aetiology, the indolent T cell large granular lymphocytic leukaemia is commonly associated with mono-cellular, bi-cellular or pancytopenia. Emerging neutropenia or anaemia mandates commencement of cogent therapy. T cell large granular lymphocytic leukaemia configures up to 5% of mature lymphocytic leukaemia and preponderantly incriminates peripheral blood, bone marrow, spleen or hepatic parenchyma. Characteristically, bone marrow, spleen or hepatic parenchyma exhibits an intra-sinusoidal pattern of tumour cell dissemination. T cell large granular lymphocytic leukaemia is frequently encountered within elderly individuals with median age of disease emergence at 60 years. An equivalent gender predisposition is observed [1,2]. T cell large granular lymphocytic leukaemia represents with oligo-clonal expansion of cytotoxic large granular T cells occurring as a consequence to antigenic stimulation. Subsequently, clonal proliferation of large granular T cells ensues on account of constitutive upregulation of signals of cellular survival accompanied by downregulation of apoptotic pathways through a secondary genetic manifestation [1,2]. Generally, genomic mutations of STAT3 or STAT5b may emerge as a secondary event. Besides, resistance to Fas / FasL mediated cellular mortality, enhanced cellular survival on account of interleukin 15 (IL15) and platelet derived growth factor (PDGF) associated with activation of nuclear factor kappa-light- chain enhancer of activated B cells (NFkB) pathway may configure as inducing secondary manifestations. Neutropenia and anaemia may occur due to direct cytotoxicity engendered from monoclonal, neoplastic T lymphocytes.

Additionally, T cell large granular lymphocytic leukaemia may arise on account of chronic antigenic exposure concurrent with autoimmune disorders as rheumatoid arthritis or Sjögren syndrome. Besides, chronic antigenic exposure may occur due to viral infection with agents such as human T- lymphotropic virus (HTLV) [1,2].

Cytogenetic analysis of T cell large granular lymphocytic leukaemia exemplifies clonal T cell receptor (TCR) genetic rearrangements along with STAT3 genetic mutation in ~50% instances and STAT5b genetic mutations in ~2% instances. However, T cell large granular lymphocytic leukaemia is devoid of specific cytogenetic abnormalities [1,2]. Majority (~70%) of subjects with T cell large granular lymphocytic leukaemia enunciate neutropenia or anaemia. Around one third (~30%) of asymptomatic subjects may demonstrate lymphocytosis with mono-cellular, bi-cellular or pancytopenia discernible upon comprehensive haematological assessment. Nearly one third (~30%) implicated subjects display splenomegaly or concurrent autoimmune disorders, generally rheumatoid

arthritis. T cell large granular lymphocytic leukaemia may be associated with diverse haematological malignancies as B cell lymphoma, myelodysplastic syndrome or aplastic anaemia [3,4].

Peripheral blood smear demonstrates an elevated lymphocyte count wherein miniature to intermediate lymphocytes are incorporated with reticulated nuclei and fine to coarse, azurophilic, cytoplasmic granules.

Upon microscopy, bone marrow biopsy appears devoid of an infiltrate of anomalous, neoplastic lymphocytes upon staining with haematoxylin and eosin. Nevertheless, immunohistochemistry characteristically exhibits a linear or intra-sinusoidal dissemination of neoplastic, cytotoxic T cells. Surgical tissue samples from spleen demonstrate linear dispersion of cytotoxic T cells confined to sinusoids and cords of red pulp. Tissue samples from hepatic parenchyma exemplify linear distribution of cytotoxic T cells confined to hepatic sinusoids [3,4] (Figure 1 & 2; Table 1 & 2).

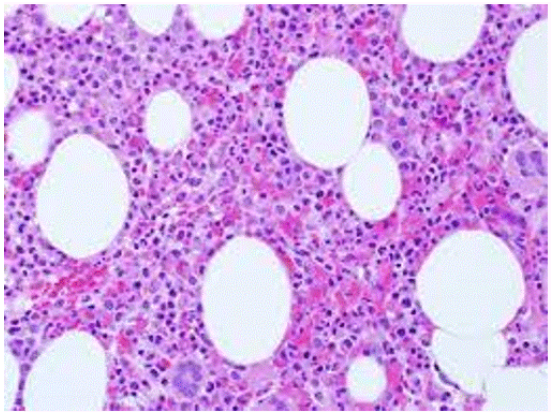

Figure 1: T cell large granular lymphocytic leukaemia delineating intra-sinusoidal pattern of neoplastic cellular dissemination with pancytopenia [6].

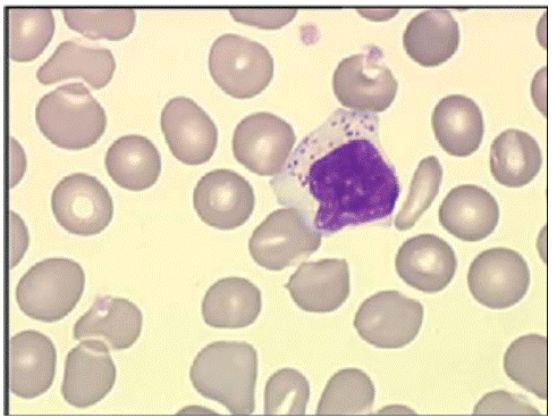

Figure 2: T cell large granular lymphocytic leukaemia demonstrating intermediate, neoplastic lymphocytes with reticulated nuclei and fine to coarse intracytoplasmic granules [7].

Table 1: Classification of T cell large granular lymphocytic leukaemia as per World Health Organization classification (2016) [5].

Mature T cell/NK cell neoplasms
T cell granular lymphocytic leukaemia
Aggressive NK cell leukaemia
Chronic lymphoproliferative disorder of NK cells

Occurrence of STAT3 and STAT5b mutations may occur in a subset of leukaemia and appear associated with clinically aggressive disease

Table 2: Disorders associated with large granular lymphocytic leukaemia [5].

Neoplasms
Autoimmune cytopenias
Pure red cell aplasia
Autoimmune haemolytic anaemia
Idiopathic thrombocytopenic purpura
Evans syndrome
B cell lymphoid neoplasms
Low grade non Hodgkin's lymphoma
Diffuse large B cell lymphoma
Mantle cell lymphoma
Multiple myeloma
Chronic lymphocytic leukaemia
Hairy cell leukaemia
Waldenström macroglobulinaemia
Hodgkin's lymphoma
Lymphomatoid granulomatosis
Heavy chain disease
Autoimmune diseases/connective tissue disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Vasculitis
Systemic sclerosis
Endocrinopathy
APECED(polyendocrinopathy candidosis-ectodermal dystrophy)
Multiple endocrine neoplasia-1
Hashimoto's disease
Graves' disease
Chronic inflammatory bowel disease
Coeliac disease
Gougerot-Sjögren syndrome
Glomerulonephritis
Polymyositis
Inclusion body myositis
Poly/multinevritis
Rhizomelic pseudo-polyarthritis
Inflammatory arthritis(unclassified)
Lambert-Eaton myasthenic syndrome
Good syndrome
Behcet's disease
Multiple sclerosis
Acquired factor VIII inhibitor
Myelodysplastic syndrome
Acute myeloid leukaemia
Haemophagocytic syndrome
Pulmonary hypertension
Post-organ or haematopoietic stem cell transplantation
Post viral infection

T cell large granular lymphocytic leukaemia is variably immune reactive to CD2, CD3, CD5, CD7, CD8, CD16, CD56, CD57, CD94, killer cell immunoglobulin-like receptor (KIR) isoform restriction, granzyme B, granzyme M , T cell intracellular antigen 1(TIA1) or T cell receptor alpha/beta (TCRαβ). Neoplastic cells are infrequently immune reactive to T cell receptor gamma/delta (TCRγδ) or CD4 [3,4]. T cell large granular lymphocytic leukaemia is immune non reactive to terminal deoxynucleotidyl transferase (TdT), CD1a or CD10.

Upon flow cytometry, T cell large granular lymphocytic leukaemia represents with mature CD3+ T cells which may co-express NK cell immune markers as CD16 or CD57. Besides, variable expression of pan T cell markers as CD2, CD5, CD7 may be discerned. An estimated 25% instances are killer cell immunoglobulin-like receptor (KIR) restricted [3,4]. Neoplastic cells predominantly depict a CD4-/ CD8+ T cell immuno-phenotype along with T cell receptor gamma/delta (TCRγδ+) T cell subtype, CD4+/ CD8- T cell subtype, T cell receptor alpha/beta (TCRαβ+) T cell subtype, CD4-/ CD8- T cell subtype or an exceptionally discerned mixed immuno-phenotype [3,4]. T cell large granular lymphocytic leukaemia requires segregation from conditions such reactive T cell expansion confined to lymph node, chronic lymphoproliferative disorder of NK cells, peripheral T cell lymphoma or hepatosplenic T cell lymphoma [3,4]. T cell large granular lymphocytic leukaemia delineates a persistent (>6 months) elevation of quantifiable peripheral blood large granular lymphocytes which vary from 2 $x10^9$/litre to 20 x 10^9/ litre. The leukaemia demonstrates a distinct T cell population which expresses ≥ one NK cell antigens as CD16, CD56 or CD57 along with decimated expression of CD2, CD5 or CD7. Emergence of T cell monoclonal population may be confirmed with cogent molecular analysis or flow cytometry assessment [3,4]. Intra-sinusoidal cytotoxic T cells appear to infiltrate bone marrow, spleen or hepatic parenchyma. Neoplastic T cells demonstrate STAT3 or STAT5b genetic mutation [3,4]. Haematological evaluation exhibits variable lymphocytosis. Majority of instances depict neutropenia (85%) along with anaemia (50%), pure red cell aplasia (10%) and thrombocytopenia in < 25% subjects. Incriminated individuals may be immune reactive to rheumatoid factor and exhibit antinuclear antibodies. T cell large granular lymphocytic leukaemia is associated with splenomegaly (30%), hepatomegaly (< 30%) and exceptionally demonstrates regional lymph node enlargement [3,4]. Majority of implicated individuals necessitate treatment on account of severe or symptomatic neutropenia or anaemia. However, standardized therapeutic guidelines for managing T cell large granular leukaemia remain unestablished.

Immunosuppressive therapy comprised of methotrexate, cyclophosphamide or cyclosporine may be beneficially adopted as initial therapeutic agents [3,4]. Generally, T cell large granular lymphocytic leukaemia is an indolent disease wherein disease associated mortality is infrequently associated with infections incurred due to severe neutropenia. Additionally, STAT3 / STAT5b genetic mutations may induce an adverse influence upon overall survival [3,4].

Acknowledgements

None.

Conflict of Interest

Author declares there is no conflict of interest.

References

1. Abu Rous F, Gutta R, Chacko R, Kuriakose P, Dabak V. Unusual Presentation of T-cell Large Granular Lymphocytic Leukemia. Cureus. 2022; 14(7): e26742.
2. Gorodetskiy V, Sidorova Y, Biderman B, Kupryshina N, Ryzhikova N, Sudarikov A. STAT3 mutations in “gray-zone” cases of T-cell large granular lymphocytic leukemia associated with autoimmune rheumatic diseases. Front Med (Lausanne). 2022; 9: 1000265.
3. Schreiber J, Pichler A, Kornauth C, Kaufmann H, Staber PB, Hopfinger G. T-Cell Large Granular Lymphocyte Leukemia: An Interdisciplinary Issue? Front Oncol. 2022; 12: 805449.
4. Chin-Yee B, Suthakaran A, Hedley BD, Howlett C, Stuart A, Sadikovic B, et al. T-cell clonality testing for the diagnosis of T-cell large granular lymphocytic leukemia: Are we identifying pathology or incidental clones? Int J Lab Hematol. 2022; 44(6): 1115-1120.
5. Lamy T, Moignet A, Loughran TP Jr. LGL leukemia: from pathogenesis to treatment. Blood. 2017; 129(9): 1082-1094.
6. Image 1 Courtesy: Pathology outlines.
7. Image 2 Courtesy: Semantic Scholar.