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Case Report

Tracing absolute lymphocytosis to T-large granular lymphocytic leukaemia in elderly: a flowcytometry based case report

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ABSTRACT

T-cell large granular lymphocytic leukaemia (T-LGL leukaemia) is a rare, neoplastic proliferation of cytotoxic T cells, accounting for less than 5% of all chronic lymphoproliferative disease. Diagnosing T-LGLL can be challenging, particularly in distinguishing it from reactive lymphocytosis. Despite its indolent nature, T-LGL leukaemia remains incurable, highlighting the need for improved therapeutic strategies. The TRBC1 flow cytometric assay provides a rapid and reliable means of assessing T-cell clonality in patients with large granular lymphocytosis, facilitating diagnosis through detection of altered proportions of TRBC1^{+} αβ T cells. We report a case of T-LGL leukaemia with an immunophenotypic clonal T-cell, characterised as a CD4-/CD8+ T-cell, TCRαβ subset, exhibiting downregulation of CD5 and CD7, with expression of the NK Cell marker CD16.

Keywords: T-Large granular lymphocyte leukaemia, TRBC1, Large granular lymphocytes, Flowcytometry, Chronic lymphoproliferative disease

INTRODUCTION

T-cell large granular lymphocytic leukaemia (T-LGLL) is a rare chronic mature lymphoproliferative disorder, accounting for approximately 2-3% of all lymphoid malignancies.[1,2] The 5th WHO hematolymphoid edition describes T-LGLL as a neoplastic proliferation with persistent absolute lymphocytosis of >2×10^{6}/L of the cytotoxic large granular T cells.[3] It is frequently associated with autoimmune disorders, with frequent association with HTLV that exemplifies the principal role of chronic antigenic stimulation.[3] Cytotoxic (CD8+) T cells proliferate clonally and clinically, as lymphocytosis with neutropenia, anaemia, and/or thrombocytopenia.[4]

The aetiology of TLGL leukaemia is complex, involving neoplastic, viral, and autoimmune mechanisms, typified by underlying molecular and systemic disorders.[3,5] Activation or mutation of the STAT3 pathway plays a pivotal role in the pathogenesis and clonal expansion of LGLs, marking a key advancement in understanding the disease biology.[5] Despite its indolent nature, T-LGL leukaemia remains incurable, highlighting the need for improved early diagnostic modalities and therapeutic strategies.

Immunophenotypic characterisation is essential for identifying and confirming the presence of clonal atypical lymphocytes. Here, we present a case of T-LGLL in an elderly male diagnosed by multiparametric flow cytometry with an illustration of the clonal T-cell population using TRBC1 antibody.

CASE REPORT

Elderly 80-year-old male with complaints of dizziness, multiple episodes of vomiting and decreased oral intake was referred for diagnostic workup of lymphocytosis. Complete blood counts revealed leucocytosis (TLC of 46050/ul) with 98% lymphocytes and anaemia with a

haemoglobin level of 7.9 g/dl. Absolute lymphocytosis (ALC=44,240/ul) and moderate neutropenia (ANC=900/ul) were also observed. Platelet counts were within normal limits. There was a history of single unit transfusion of packed RBC for anaemia. Giemsa-stained slides of the peripheral blood revealed a predominant lymphocyte population, consisting of medium to large atypical lymphocytes. These atypical lymphocytes showed an abundant cytoplasm with distinct coarse azurophilic granules, medium with minimally irregular nuclei and condensed chromatin (Figure 1). No significant history of autoimmune disorders was present.

Multiparametric flowcytometric analysis was done for the characterisation of atypical lymphocytes in the peripheral blood sample. The samples were processed using Stain-Lyse-Wash and analysed using the BD FACSLyric and BD FACSuite software. A set of antibodies along with their clones is CD45 (2D1), CD3 (clone SK7), CD56 (clone NCAM16.2), CD16 (clone 3G8), CD4 (clone SK3), CD8 (clone SK1), CD7(clone M-T701 (RUO)), CD5 (clone L17F12), CD57 (clone HNK-1), TCR-β1 (clone JOV 1) were utilised for the case. B- CLPD markers were used to rule out B-chronic lymphoproliferative disorders. A gating strategy using CD45 bright vs low side scatter was employed to analyse the lymphocyte population.

Immunophenotyping by flow cytometry gated 90% lymphocytes, of which 99% of the gated lymphocytes revealed an effector clonal TCRαβ+ large cytotoxic T cell population with downregulation of CD5 and CD7. These atypical lymphocytes were bright positive for CD45, CD3, and CD8, along with dim to moderate positivity of CD5, CD7 and CD16. CD4 and CD56 were negative. Further, these cells were negative for TRBC-1 (Figure 2). A final diagnosis of TLGL leukaemia was rendered, explaining the cause of lymphocytosis in this patient.

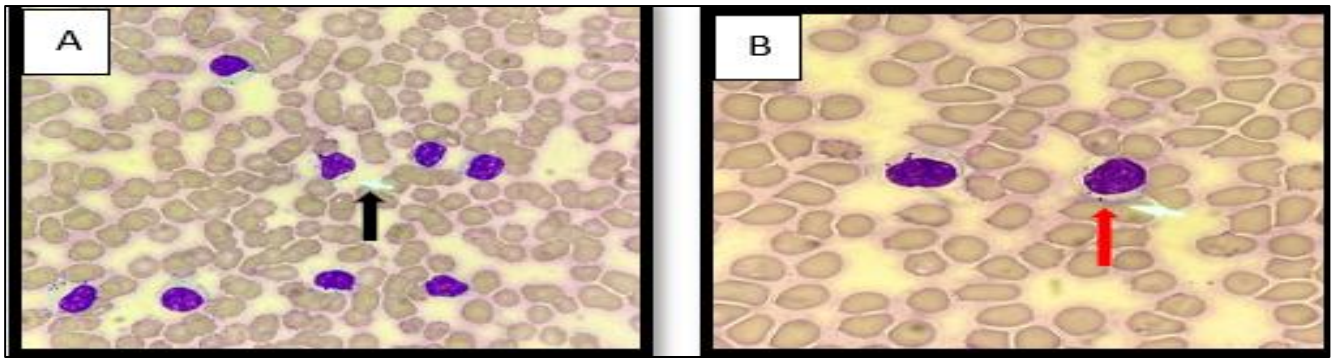

Figure 1 (A and B): A-Giemsa stained peripheral smear displaying multiple large granular lymphocytes (40×, black arrow); B-Distinct coarse azurophilic granules in the cytoplasm of the lymphocyte (100×, red arrow).

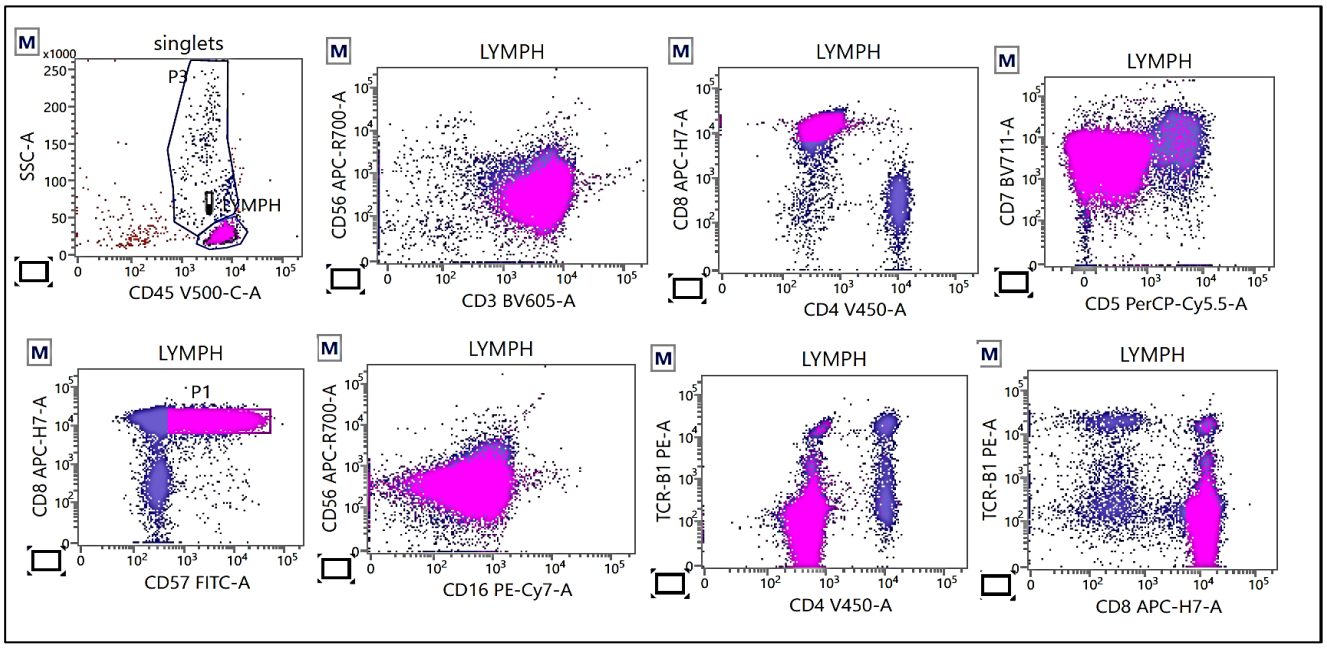

Figure 2: Multiparametric flowcytometry using bright CD45 vs SSC as the gating strategy. Clonal T-cells showing CD4- CD8+ CD7+ CD57+ CD16+ CD56-TRBC1-ve.

DISCUSSION

First described in 1985, LGL leukaemia is a rare chronic mature lymphoproliferative disorder of the T/natural killer (NK) lineage.[1] It constitutes about 5-6% in Asia, with a lower incidence of 2 to 5% of chronic lymphoproliferative disorders in North America and Europe. The 2001 edition of WHO recognised T-LGLL as a distinct entity under mature T cell neoplasm. The 5th edition has incorporated emerging evidence of the genetic mutation of STAT3 and its phenotypic significance in T-LGLL.[3]

T-LGL leukaemia is diagnosed by the presence of two or all three essential criteria, consisting of an increased circulating T cell count, greater than 2000/ul, with an aberrant phenotype, CD8+ with downregulation of CD5 or CD7 and or aberrant expression of CD16 and NK cell-associated receptors with evidence of monoclonality. Presence of intra-sinusoidal cytotoxic T cells in bone marrow by IHC, STAT3 mutation is a desirable criterion for the diagnosis of T-LGL.[3] Adults aged 45 to 75 years are commonly affected. A strong association with autoimmune diseases, especially rheumatoid arthritis, is noted.[6,7]

The patient in our report was an elderly male of 80 years old with a nonspecific clinical presentation of weakness and dizziness. Diagnostic workup of the peripheral blood revealed lymphocytosis with predominant LGLs, and further investigation with viral, serological and dengue ruled out reactive causes of lymphocytosis. Multiparametric flow cytometry characterised these atypical lymphocytes as an effector clonal TCRαβ+ large cytotoxic T cell population with downregulation of CD5, CD7 and expression of CD16.

The peripheral blood in T-LGL leukaemia reveals an increasing number of LGL count (>2000/uL), cytopenia (most commonly neutropenia) and anaemia, with no significant change in the platelet count.[3] In cases of low absolute count of LGL, a combination of other criteria may be compatible with the diagnosis.[8-10] Morphologically, the lymphocytes display a large size and an abundant cytoplasm containing typical azurophilic granules with mature chromatin. More than 50% of the cases may show hyperplasia of lymphocytes in the bone marrow aspirate. Granular lymphocytosis may also be observed in spleen.[11] The peripheral blood smear of this patient showed lymphocytosis consisting predominantly of atypical lymphocytes displaying coarse azurophilic granules in the cytoplasm. Flowcytometry is critical to rule out benign, reactive expansions of cytotoxic lymphocytes and aggressive neoplasms of cytotoxic lymphocytes that can involve blood and bone marrow, such as Hepatosplenic T cell leukaemia and aggressive NK-cell leukaemia.

Immunophenotypically, T-LGL cells display a mature post-thymic phenotype, and most frequently show CD3+, TCRαβ+, CD8+, CD16+, CD45RA+, and CD57+. CD4, CD5, CD27, CD28, and CD45RO are usually negative. NK K-LGL cells, on the other hand, are CD3-, TCRαβ-, CD2-, CD4-, CD8+, CD16+, CD94+, and CD56+.[12] Although clonal, LGL leukemic cells may exhibit heterogeneity between patients with varying phenotypes. A distinct LGL leukaemia phenotype, CD3+CD4+CD8+CD56+, may also have characteristic STAT5B mutations, with an indolent clinical course.[5] CD56 expression in T-LGL cells may have more aggressive clinical behaviour and has been associated with mutations of the STAT5B gene.[13,14] Clonality of the LGL cells is essential to categorise this lymphoproliferation as leukaemia and distinguish it from autoimmune or infectious disease. Clonality of T-LGL cells can be established with PCR with probes for T-cell receptor (TCR).[15]Alternatively, immunophenotyping assessment of T cell clonality can be utilised with the TRBC1/TRBC2 FCM assay in suspected cases of T-LGLL based on altered percentages of TRBC1/TRBC2 cells.[16] The TRBC1/2 - FCM assay is a rapid assessment of T-cell clonality in the blood of individuals presenting with LGL lymphocytosis, unlike PCR or IHC assessment, which usually takes a longer time. Our case had a clonal T cell, an effector clonal (TRBC-1 Negative) TCR αβ+ large cytotoxic T cell population with downregulation of CD5 and CD7, with expression of NK cell marker-CD16.

Immunosuppressive therapy is the standard treatment for TLGL leukaemia; recommendations, however, are primarily based on small retrospective series. Treatment is recommended for severe neutropenia (absolute neutrophil count [ANC] <0.5×109/L), moderate neutropenia (ANC >0.5×109/L) associated with recurrent infections, symptomatic or transfusion-dependent anaemia, and associated autoimmune conditions requiring therapy.[17]

CONCLUSION

T-LGLL is a rare chronic mature lymphoproliferative disorder. Diagnosing T-LGLL can be challenging, particularly in distinguishing it from reactive lymphocytosis. The TRBC1/2 flow cytometry (TRBC1/2-FCM) assay is a rapid and reliable method for assessing T-cell clonality in patients with LGL lymphocytosis, aiding diagnosis by demonstrating altered proportions of TRBC1/2.

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