Tislelizumab and Pentostatin therapy reverse aggressive T-LGLL with near tetraploid karyotype

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Dear Editor,

T-cell large granular lymphocytic leukemia is an indolent leukemia with no standard treatment for its aggressive variants. We report a 26-year-old Chinese male with T-cell Large Granular Lymphocyte Leukemia (T-LGLL) progressing to aggressive T-LGLL with a near tetraploid karyotype. After conventional chemotherapy failed, he achieved complete remission with Tislelizumab and Pentostatin. No relapse occurred during six months of follow-up, suggesting a potential role for immunotherapy in managing aggressive T-LGLL.

CASE PRESENTATION

A 26-year-old Chinese man presented with a one-week history of sternal pain, accompanied by fatigue and night sweats. Physical examination revealed cervical lymphadenopathy and splenomegaly, with ultrasound showing a spleen thickness of 59 mm. Laboratory tests indicated pancytopenia, with platelet count (Plt) of 90×10^9/L, neutrophil count (Neu) of 1.15×10^9/L, and hemoglobin (Hb) level of 121 g/L. A clinical timeline is shown in Figure 1A. Bone marrow aspirate (BMA, Figure 1B) showed 55% T-cell large granular lymphocytes (T-LGL). Immunophenotyping revealed 63.42% atypical $CD8^+$ T cells (TCR $\alpha\beta^+$, $CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, $CD57^+$, TCR $\gamma\delta^-$, $CD4^-$, $CD30^-$, $CD56^-$, $Ki67^-$). Initial TCR vβ clonality analysis: peripheral blood lymphocytes were 51.66% of nucleated cells, 29.76% being $CD8^+$ T cells (79.9% TCR $v\beta1^+$), confirming a monoclonal T cell population. A bone marrow biopsy (BMB, Figure 1C) confirmed peripheral T-cell lymphoma infiltrating the marrow, with a diffuse infiltration pattern of large atypical T cells. The immunophenotype was $CD3^+$, $CD20^-$, $CD5^+$, $CD2^+$, $CD7^+$, $CD4^-$, $CD8^+$, $CD57^-$, CD30partial$^+$, $CD21^-$, $CD56^-$, TCL-1^-, and Epstein-Barr virus-encoded RNA (EBER)$^-$. According to the 5th edition of the World Health Organization (WHO) and International Consensus Classification (ICC) classifications, these findings were consistent with T-cell large granular lymphocytic leukemia (T-LGLL), an indolent cytotoxic T-cell neoplasm characterized by persistent cytopenia and the presence of LGLs with a mature $CD3^+$ $CD8^+$ $CD57^+$ phenotype.[1,2] Next-generation sequencing of a 214-gene panel, including *STAT3*, *TP53* and *TET2*, revealed no pathogenic mutations. After eight months of cyclosporine therapy, the patient developed severe pancytopenia (Plt, 34×10^9/L; Neu, 0/L; Hb, 68 g/L). A computed tomography (CT) scan at disease progression also revealed worsened splenomegaly (thickness = 95 mm), an enlarged porta hepatis lymph node measuring approximately 12 × 15 mm, and multiple retroperitoneal lymph nodes with a maximum short-axis diameter of 9.5 mm. Approximately 20% of lymphoma cells were found in BMA (Figure 1D), and karyotyping revealed complex numerical abnormalities (90–91<4n>, XXYY, inc [5]/46, XY, Figure 1E). Flow cytometry identified 38.9% of lymphoid cells as atypical $CD8^+$ T cells, exhibiting a TCR $\alpha\beta^+$, $CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, $CD57^+$, CD279partial$^+$, TCR $\gamma\delta^-$, $CD56^-$, $CD34^-$, $CD30^-$, $CD10^-$, $CD161^-$, $CD16^-$, $CD94^-$, $CD25^-$, $Ki67^-$, $CD45RA^-$ profile. BMB showed peripheral T-cell lymphoma involving the marrow with a $CD3^+$, $CD20^-$, $CD4^-$, $CD5^+$, $CD8^+$, TIA-1^+, $CD57^-$, $CD30^-$, $CD21^-$, $CD56^-$, $EBER^-$ phenotype. Flow cytometry showed 79.71% $CD8^+$ T cells had TCR vβ restriction, confirming clonal cytotoxic T cell proliferation consistent with indolent T-LGLL transforming to aggressive peripheral T-cell lymphoma. After two courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and Hyper-CVAD (Hyperfractionated, Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone) chemotherapy, neutrophil counts remained zero, indicating refractory disease.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for T Cell Lymphomas recognize purine analogs as a therapeutic option for LGLL.[3] Given this recommendation and the patient's $CD279^+$ (Programmed cell death protein 1, PD-1) expression profile, combination therapy was initiated. Consequently, the patient received the PD-1 inhibitor Tislelizumab (200 mg IV every 3 weeks) alongside the purine analog Pentostatin (4 mg/m^2 IV weekly). After two doses of Tislelizumab and four doses of Pentostatin, symptoms improved, and blood counts normalized. Repeat BMA showed complete remission, with flow cytometry negative for residual T-LGL cells and a normal karyotype (Figures 1F-G). Consolidation therapy continued with Tislelizumab (200 mg intravenously every 3 weeks) and Methotrexate (40 mg intramuscularly weekly). At two-month follow-up, the patient maintained remission with 0.90% abnormal T cells. By six months, he sustained a complete hematologic response with normalized blood counts. Following one year of monthly PD-1 inhibitor maintenance (200 mg), he remains event-free at the three-year follow-up, with quarterly follow-ups and assessments.

DISCUSSION

The patient's initial presentation fulfilled the WHO 5th edition and ICC criteria for T-LGLL, featuring cytopenia, bone marrow infiltration by mature cytotoxic $CD8^+$ T cells, and a low proliferative index without destructive tissue involvement. With disease progression, progressive cytopenia, diffuse marrow infiltration, lymphadenopathy, and a markedly atypical near-tetraploid karyotype signaled T-LGLL progression from indolent to aggressive T-cell lymphoma. Rare in chronic T-cell neoplasms, such transformation usually links to high proliferation, complex cytogenetics, and poor prognosis.[4] Therapeutic options include purine analogs, bendamustine, or alemtuzumab, often followed by hematopoietic stem cell transplantation (HSCT).[5] To the best of our knowledge, T-LGLL cases with polyploid or near-tetraploid karyotypes are extremely rare. Only a few such cases have been previously reported in the literature, all of which were associated with unfavorable outcomes.[4,6] One case involved a 55-year-old woman whose isolated lymphocytosis progressed over two years to symptomatic disease with lymphadenopathy and a hyperploid karyotype harboring 17p deletion. Despite multiple chemotherapy regimens and transient remission after high-dose methotrexate and L-asparaginase, she relapsed and died post-transplantation. Another case involved a 75-year-old woman with chronic neutropenia who eventually developed lymphadenopathy and subcutaneous nodules with LGL infiltration. Her karyotype demonstrated profound chromosomal instability, characterized by multiple numerical aberrations—including various monosomies and trisomies—and complex structural rearrangements. Despite methotrexate, alemtuzumab, and intensive chemotherapy, she succumbed to multi-organ failure. Collectively, these cases demonstrate that polyploid or near-tetraploid karyotypes in T-LGLL confer resistance to therapy and a dismal prognosis.

This case is unique in describing T-LGLL progression to aggressive T-cell lymphoma with a near-tetraploid karyotype. This cytogenetic abnormality signals profound genetic instability that drives clonal evolution and drug resistance, exerting adverse effects through multiple interconnected mechanisms: it correlates with increased chromosomal instability, which fuels tumor heterogeneity and aggressiveness; induces replication stress that causes Deoxyribonucleic acid (DNA) damage and mitotic error; and is associated with loss of p53 and other cell cycle checkpoint regulators, enabling genomically unstable cells to escape surveillance and proliferate uncontrollably.[7] Relevant findings in other hematologic malignancies support this

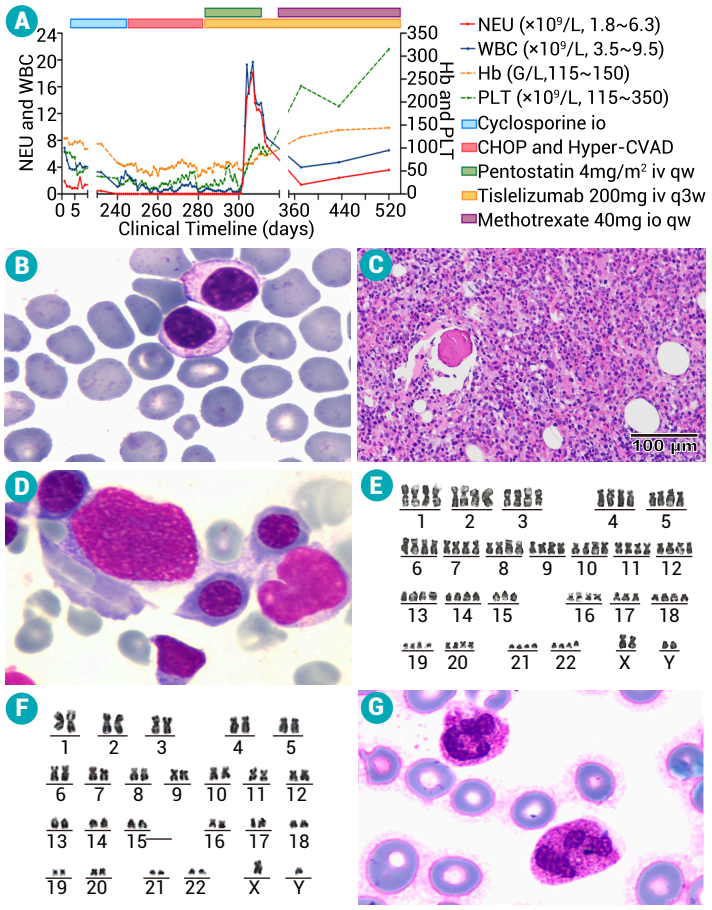

Figure 1. Clinical and cytogenetic evolution of T-LGLL throughout treatment (A) Clinical timeline depicting changes in NEU, WBC, Hb, and PLT counts in relation to treatment interventions. The left y-axis represents NEU and WBC counts (×10^9/L), and the right y-axis represents Hb (g/L) and PLT (×10^9/L). The x-axis indicates the clinical follow-up period (days). Colored bars above the graph indicate the timing of chemotherapy and immunosuppressive regimens. (B) Bone marrow aspirate (May–Grünwald–Giemsa stain; ×1000) at diagnosis showing large granular lymphocytes with azurophilic granules, characteristic of T-LGLL. (C) Bone marrow biopsy (Hematoxylin and eosin stain; ×200) at diagnosis displaying diffuse infiltration of atypical T lymphocytes. (D) Bone marrow aspirate (May–Grünwald–Giemsa stain; ×1000) during progression following cyclosporine therapy. (E) Conventional cytogenetic analysis at progression revealing a hyperdiploid/tetraploid clone (90–91<4n>, XXYY, inc[5]/46,XY). (F) Cytogenetic analysis at remission demonstrating a normal male karyotype (46,XY). (G) Peripheral blood smear (May–Grünwald–Giemsa stain; ×1000) at remission showing normalized hematopoiesis. Abbreviations: NEU, neutrophil; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; T-LGLL, T-cell large granular lymphocyte leukemia; P.O., per os (oral administration); i.v., intravenous; q.w., once weekly; q3w, once every three weeks.

observation: in chronic lymphocytic leukemia, near-tetraploidy independently predicts Richter transformation;[8] prognostically, it aligns with tetraploid/near-tetraploid acute myeloid leukemia, where the median overall survival is only 4.5–5 months, and even shorter (3.4 months) for variants with complex abnormalities.[9] Consistently, such cytogenetic aberrations in T-LGLL confer marked chemoresistance and an extremely dismal prognosis.

Moreover, the patient's PD-1 expression highlights a potential pathogenic and therapeutic relevance. Although PD-1 is typically associated with T-follicular helper (TFH)-like T-cell lymphomas—characterized by CD4$^+$ phenotype and co-expression of CD10, BCL6, PD-1, CXCL13, and ICOS per the WHO 5th edition—its presence in T-LGLL is rare and may indicate responsiveness to PD-1 blockade. Remarkably, the patient achieved complete remission with Tislelizumab, a PD-1 inhibitor, combined with Pentostatin, a purine analog. We propose that this regimen provided complementary and synergistic effects: Pentostatin suppresses clonally expanded T cells by inhibiting adenosine deaminase, lowering tumor burden, relieving immunosuppression, and enabling immune reconstitution. T-LGLL inherently has T-cell exhaustion: single-cell sequencing confirms its cytotoxic clonotypes overexpress exhaustion markers, promoting persistence. Tislelizumab acts dually: reversing malignant T-cell exhaustion and activating bystander CD8$^+$ T/NK cells. It restores PD-1-suppressed NK cell function, critical for efficacy. Their synergy—Pentostatin restoring immune homeostasis, Tislelizumab reactivating effectors—enables immune cells to clear minimal residual disease (MRD) and boost anti-tumor surveillance.[10] This dual mechanism—simultaneously targeting the malignant clone and reinvigorating the immune microenvironment—may have contributed to the rapid hematologic recovery and durable remission observed. However, as this is a single case, the efficacy and safety of PD-1 blockade combined with purine analogs in T-LGLL warrant validation in larger cohorts. Nonetheless, our findings raise the possibility that a potential therapeutic option, especially for patients with high-risk cytogenetic features such as near-tetraploidy. The patient's response further underscores the importance of personalized therapies, particularly in cases with complex cytogenetic profiles, offering hope for better outcomes in this refractory malignancy.

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AUTHOR CONTRIBUTIONS

YHC contributed to data collection and manuscript writing. LVT revised the submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

We confirm that all methods involving human subjects were conducted in accordance with the relevant guidelines and regulations of the Human Ethics Committee. The protocol was reviewed and approved by the Ethics Committee of Union Hospital, Huazhong University of Science and Technology, Wuhan, China (No. 2024-0715), in compliance with applicable guidelines and regulations. Written informed consent was obtained from the patient prior to participation.