A Case of CD4⁺T-Cell Large Granular Lymphocytic Leukemia

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We report here a case of a 59-yr-old man with CD4⁺ T-cell large granular lymphocytic leukemia (T-LGL). Peripheral blood examination indicated leukocytosis (45 × 10⁹ cells/L) that consisted of 34% neoplastic lymphoid cells. Other laboratory results indicated no specific abnormalities except for serum antinuclear antibody titer (1:640), glucose (1.39 g/L), and hemoglobin A1c (7.7%) levels. Computed tomography indicated multiple small enlarged lymph nodes (<1 cm in diameter) in both the axillary and inguinal areas, a cutaneous nodule (1.5 cm in diameter) in the left suboccipital area, and mild hepatosplenomegaly. Bone marrow examination revealed hypercellular marrow that consisted of 2.4% neoplastic lymphoid cells. The neoplastic lymphoid cells exhibited a medium size, irregularly shaped nuclei, a moderate amount of cytoplasm, and large granules in the cytoplasm. Immunohistochemical analysis indicated CD3⁺, CD4⁺, T-cell receptor βF1⁺, granzyme B⁺, and TIA1⁺. Flow cytometric analysis of the neoplastic lymphoid cells revealed CD3⁺, cytoplasmic CD3⁺, CD4⁺, and CD7⁺. Cytogenetic analysis indicated an abnormal karyotype of 46,XY,inv(3)(p21q27),t(12;17)(q24.1;q21),del(13)(q14q22)[2]/46,XY[28]. The patient was diagnosed with CD4⁺ T-LGL and received chemotherapy (10.0 mg methotrexate). This is the second case of CD4⁺ T-LGL that has been reported in Korea.

Key Words: CD4⁺ T-LGL skin lesion, Leukocytosis

INTRODUCTION

T-cell large granular lymphocytic leukemia (T-LGL) is a heterogeneous disorder that is characterized by the expansion of a discrete or monoclonal population of large granular lymphocytes in the peripheral blood (PB) [1].

T-LGL usually expresses CD3, CD8, and T-cell receptor (TCR) αβ. CD5 and/or CD7 are variably expressed and are often aberrantly diminished on malignant circulating LGL cells [2, 3]. T-LGL typically expresses cytotoxic granular proteins such as TIA1, granzyme B, and granzyme M [4, 5]. Immunohistochemical analysis of bone marrow (BM) biopsies with antibodies to these antigens and CD8 can be used to confirm a diagnosis of T-LGL [4-6]. The clinical course of T-LGL is indolent in most cases [7]. CD8⁺ T-LGL is associated with mild to moderately stable lymphocytosis, neutropenia, splenomegaly, and occasionally anemia [8]. Lymphadenopathy is very rare [9]. In addition, T-LGL demonstrates a strong association with autoimmune diseases, especially rheumatoid arthritis [8].

In contrast, the monoclonal expansion of CD4⁺ T-LGL has been reported only sporadically in the literature [7]. It is marked by its association with malignant diseases and characteristically shows the absence of cytopenia, splenomegaly, and autoimmune disease [7]. Here, we report a case of CD4⁺ T-LGL.
CASE REPORT

A 59-yr-old man with a skin rash that had been present for 6 months was admitted to the hospital for an evaluation. He was diagnosed with hypertension and diabetes mellitus. PB examination revealed the following: white blood cell count, \(4.5 \times 10^9\) cells/L (consisting of 34% neoplastic lymphoid cells, 10% segmented neutrophils, 47% lymphocytes, 6% monocytes, and 3% eosinophils); hemoglobin, 131 g/L; mean corpuscular volume, 90.9 fl; and \(4.19 \times 10^9\) platelets/L. Neoplastic lymphoid cells displayed large granules (Fig. 1). PB neoplastic lymphoid cells were surface CD3\(^+\), cytoplasmic CD3\(^+\), CD4\(^+\), CD7\(^+\), CD8\(^-\), CD16\(^-\),

![Fig. 1. Neoplastic lymphoid cells. (A) The neoplastic lymphoid cells with large cytoplasmic granules in the peripheral blood (Wright-Giemsa stain, \(\times1,000\)). (B) The neoplastic lymphoid cells in bone marrow aspirates with a medium, irregularly shaped nuclei, a moderate amount of cytoplasm, and large cytoplasmic granules (Wright-Giemsa stain, \(\times1,000\)).](image)

![Fig. 2. Immunophenotyping of neoplastic lymphoid cells in peripheral blood by flow cytometry. (A) Gating of neoplastic lymphoid cells with bright CD45 expression and low SSC, (B) CD4 positivity (96% among gated cells) and CD8 negativity, (C) surface CD3 positivity (95%), (D) cytoplasmic CD3 positivity (93%), and (E) CD7 positivity (73%). Abbreviations: SSC, side scatter characteristics; FSC, forward scatter characteristics.](image)
CD19, CD20, and CD56 (Fig. 2). Other laboratory results included the following: serum antinuclear antibody titer, 1:640; glucose, 1.39 g/L; hemoglobin A1c, 7.7%; total protein/albumin, 7.1/3.9 g/dL; AST/ALT, 12/12 IU/L; and total bilirubin, 5 g/L. Multiple small enlarged lymph nodes (<1 cm in diameter) in both the inguinal and axillary areas, and mild hepatosplenomegaly were noted on the abdominal and pelvic computed tomography (CT) scans. A cutaneous nodule (1.5 cm in diameter) was also observed in the left suboccipital area, but this seemed to be a reactive enlargement of the lymph nodes. BM study revealed hypercellular marrow that consisted of 2.4% neoplastic lymphoid cells. The neoplastic lymphoid cells exhibited a medium size, irregularly shaped nuclei, a moderate amount of cytoplasm, and large granules in the cytoplasm (Fig. 1). Immunohistochemical analysis of the BM biopsy showed CD3+, CD4+, TCR βF1+, granzyme B+, and TIA1+ (Fig. 3). TCR γ gene rearrangement by BIOMED-2 PCR assays (InVivoScribe, San Diego, CA, USA) was negative. Cytogenetic analysis indicated an abnormal karyotype: 46,XY,inv(3)(p21q27),t(12;17)(q24.1;q21),del(13)(q14q22)[2]/46,XY[28]. The patient was diagnosed with CD4+ T-LGL and received chemotherapy (10.0 mg methotrexate/week for 4 months). After the treatment, PB examination indicated the following values: white blood cell count, 24×10⁸ cells/L with 25% neoplastic lymphoid cells; hemoglobin, 137 g/L; and 395×10⁸ platelets/L. The patient tolerated the treatment well, and his skin lesions improved.

DISCUSSION

T-LGL represents 2% of the cases of monoclonal proliferation of B cell, T cell, and natural killer cell mature lymphocytic leukemia in Western countries [7, 9]. The male:female ratio of the reported cases is approximately one, and the majority of cases occur in the 38-72 yr age group [9, 10]. The patient described here was a 59-yr-old man.

Despite their indolent clinical behavior, clear clinical differences exist between CD4+ T-LGL and the classical CD8+ T-LGL, particularly with regard to the absence of neutropenia, anemia, splenomegaly, rheumatoid arthritis, or other autoimmune diseases, and the higher incidence of association with malignant diseases in the former group [7, 11]. In our case, neutropenia, anemia, rheumatoid arthritis, and other autoimmune diseases were absent. Although the patient demonstrated mild splenomegaly and was not diagnosed with any associated malignant diseases, our results support the notion that CD4+ T-LGL is a clonal disorder with clinicopathological characteristics that are distinct from the more common CD8+ T-LGL.

Only one case of CD4+ T-LGL displaying skin lesions has been
reported so far [7]. In our case, the patient presented with a skin lesion, and this skin lesion demonstrated atypical T-cell infiltration on skin biopsy. Generally, T-LGL involves the PB, BM, liver, and spleen, but our case supports the notion that CD4\(^+\) T-LGL can also involve the skin.

In our case, clonal T-cell proliferation was diagnosed after antinuclear antibodies were discovered, which suggests a role for the immune system in preferentially developing and expanding cytotoxic CD4\(^+\) T-cell clones. There are data that support the hypothesis that T-LGL arises from sustained immune stimulation and associated tumors [7, 9, 12, 13], but further studies are required to establish both the relationship between CD4\(^+\) T-LGL and classical CD8\(^+\) T-LGL, and the clinicopathological characteristics that distinguish these leukemias.

In conclusion, in this report we described a 59-yr-old man with CD4\(^+\) T-LGL. To the best of our knowledge, only one case of CD4\(^+\) T-LGL has been reported in Korea so far [14], and ours is the second.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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