A Case Report: Large Granular Cell Leukemia/Lymphoma (LGL)

Orhan TÜRKEN*, Ahmet ÖZTÜRK*, Bülent ORHAN**, Gökhan KANDEMİR*, Mustafa YAYLACI*

* Department of Hematology and Oncology, Gülhane Military Medical Academiy, Haydarpaşa Training Hospital,
** Ali Osman Sönmez Oncology Hospital, İstanbul, TURKEY

ABSTRACT

We presented a 64-year-old male patient with T-large granular cell leukemia/lymphoma with an agressive clinical course. Large granular lymphocytes were noted on peripheral blood smear. The phenotyping of the cells was typical T-cell lineage [CD2 (+), CD3 (+), CD5 (+)]. Clonal rearrangement of the T-cell receptor gene (TCR) was demonstrated by DNA hybridization technique. Large granular cell leukemia/lymphoma is a distinct entity with spesific clinicobiological aspects. The clinical spectrum is wide and immunophenotyping and genotyping studies need to make a diagnosis.

Key Words: Leukemia, Large granular.

Turk J Haematol 2002;19(4): 473-476

Received: *05.02.2002* ***Accepted:*** *04.06.2002*

INTRODUCTION

The term of large granular cell lymphocytic leukemia (LGL) is based on the observation of clonality and demonstration of tissue invasion by the cells which have abundant cytoplasm containing azurophilic granules in bone marrow, liver and spleen. This disease may be classified into T-cell LGL characterized by clonal CD3 (+), CD4 (-), CD8 (+), CD16 (+), CD56 (-), CD57 (+) and TCRaß (+) large granular lymphocytic proliferation of mature T-lymphocytes and natural killer (NK)-LGL characterized by CD3 (-), CD4 (-), CD8 (-), CD16 (+), CD56 (+) and CD57 (-), TCRaß (-) large granular cell proliferation of NK cell origin[1-5]. The diagnosis of LGL leukemia is suspected on the basis of a persistent express of large granular lymphocytes usually with neutropenia. Offen these lymphoproliferative disorders are associated with autoimmune diseases such as rheumatoid artritis, colitis ulserosa[6,7]. Increased frequency of various lymphoproliferative malignancies occuring in organ allograft recipient's patients has been documented[8]. These malignancies might have been associated with Epstein-Barr virus (EBV) infections and immunosupressive treatments[9-11]. Although HTLV-I and II may be associated with some cases of LGL, data indicated that most patients are not infected with HTLV-I and II virus[12,13].

A CASE REPORT

A-64-year-old male patient was admitted to the Hematology and Oncology clinic with hepatosplenomegaly, scrotal and tibial oedema, pleural effusion and lymphadenopathies on the axillary, cervical and ingu-

inal regions. Leucocytosis, anemia and trombocytopenia was detected on his complete blood count (Table 1). Large granular lymphocytes were noted on peripheral blood smear (Figure 1). Bone marrow biopsy showed hipercellularity with leukemic blasts at a high percentage. Bilaterally pleural effusion, mediastinal, axillary multiple lymphadenopathies on thorax CT and splenomegaly, paraaortic, paracaval and postpancreatic lymphadenopaties on abdominal CT were detected (Figures 2,3). Immunophenotyping showed that large granular lymphocytes were CD2 (+), CD3 (+), CD5 (+) and T-cell receptor gene rearrangement studies using DNA hybridization technique showed clonal rearrangement of T-cell receptor gene on his peripheral blood mononuclear cells. The biopsy of one of the largest cervical lymph nodes showed small lymphocytic lymphoma. Thoracal drainage for pleural effusion was performed for a few times. Treatment for large granular cell leukemia with chemotherapy including cyclophosphamide (750 mg/m^2, on day 1), doxorubicine (50 mg/m^2 on day 1), vincristine (1.4 mg/m^2 on day 1) and prednisolone (100 mg on days 1 through 5) was initiated. Chemotherapy cycles were repeated every 21 days (CHOP regimen). After three cycles, progression was detected and the patient died due to respiratory failure.

Table 1. Hematological features

WBC	(x 10^9/L)	31.1
Lympho	(x 10^9/L)	22.4
LGL	(x 10^9/L)	17.5
Plt	(x 10^9/L)	44
Hb	(g/dL)	11.3

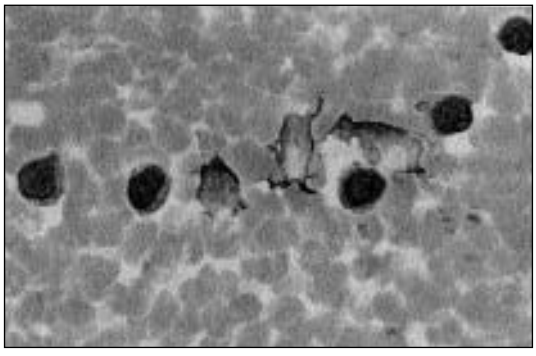

Figure 1. The appearance of peripheral blood smear.

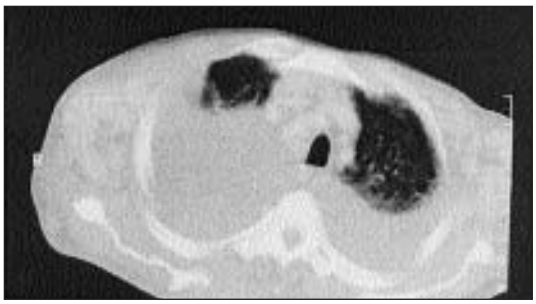

Figure 2. Bilateral pleural effusion, consolidation, multiple mediastinal and axillary lymphadenopathies on CT scan.

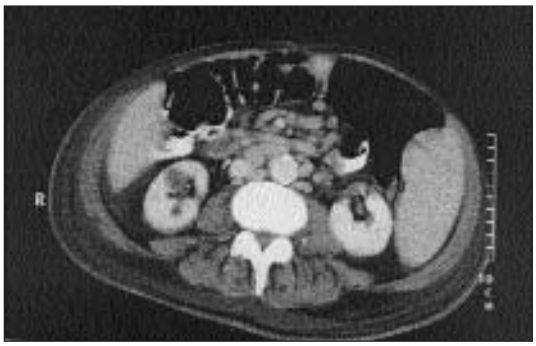

Figure 3. Splenomegaly, paraaortic, paracaval and postpancreatic lymphadenopathies on abdominal CT scan.

DISCUSSION

Large granular cell leukemia is diagnosed by increased numbers of lymphocytes and the presence of the cells that have abundant cytoplasm containing azurophilic granules but in some cases lymphocytes may appear normal and granules may be absent[14]. In our case, there were lymphocytes that have large granules and abundant cytoplasm in the peripheral blood and bone marrow. The characteristic phenotype of T-LGL was also seen on the lymphocytes and it was found that these malignant cells expressed CD2, CD3, CD5 by flow cytometry. Additionally, the patient had monoclonal T-cell gene rearrangement as a support for the diagnosis of T-LGL. The mechanism of persistent lymphocytosis in large granular cell leukemia may be in defects in CD3 activation or Fas crosslinking-induced cell death. It has been shown that inhibition of me-

talloproteinase-mediated Fas ligand solubilization or CD3 activation resulted in induction of large granular cells[15]. Clonal expansion may be facilitated by a defective apopthotic pathway and IL-2 and IL-15 cytokines expressed by leukemic cells[16-18]. Expression of Fas and FasL by leukemic cells may support the hypothesis that leukemic cells arise from antigen-activated cytotoxic T-cells and FasL may have played a role in the occurence of the clinical symptoms and could be useful as an indicator of disease activity[19]. Addition LGL cells express a multidrug-resistance phenotype that could partly explain the chemoresistance in agressive cases[16]. Although Epstein-Barr virus (EBV), Human Herpes virus type-8 (HHV8), Human T-cell leukemia-lymphoma virus-I-II (HTLV I-II) and Human immunodeficiency virus (HIV) are most implicated viruses in the pathogenesis of LGL, it was not found direct role for those viruses in the pathogenesis of T-LGL either chronic or agressive type[20-22]. Lymphoproliferative disorders of large granular lymphocytes are heterogenous clinical entities. Patients with LGL may have chronic (indolent) or agressive clinical course. Some patients may have been a long history of indolent disease before progressing to an agressive clinical course[23]. The immunophenotyping of T-LGL is CD3 (+), CD4 (-), CD8 (+), CD16 (+), CD56 (-), CD57 (+). NK-LGL cells are usually CD3 (-), CD4 (-), CD8 (-), CD16 (+), CD56 (+) and CD57 (-). Although NK-LGL has an acute fulminant course with hepatosplenomegaly, fever and pancytopenia, chronic form of disease can occur with a clinical course similar to that of T-LGL[24].

In this report, we presented a case of T-LGL with an agressive clinical course.

REFERENCES

1. Kondo H, Watanabe J, Iwasaki H. T-large granular lymphocyte leukemia accompanied by an increase of natural killer cells (CD3-) and associated with ulcerative colitis and autoimmune hepatitis. Leuk Lymphoma, 2001;41:207-12.
2. Passetto FR, Pinto SB, Garcia AB, et al. Agressive variant of morphologically typical T-large granular lymphocyte leukemia/lymphoma lacking NK cell markers. Acta Haematol 2000;104:110-4.
3. Melenhorst JJ, Sorbara L, Kirby M, et al. Large granular lymphocyte leukemia is characterized by a clonal T-cell receptor rearrangement in both memory and effector CD8 (+) lymphocyte populations. Br J Haematol 2001;112:189-94.
4. Evans HL, Burks E, Viswanatha D, et al. Utility of immunohistochemistry in bone marrow evaluation of T-lineage large granular lymphocyte leukemia. Hum Pathol 2000;31:1266-73.
5. Aslan V, Durak B, Gülbaş Z. Large granular lenfositik hastalıklar. THOD. 1999;4:226-30.
6. Blanchong CA, Olshefski R, Kahwash S. Large granular lymphocyte leukemia: A case report of chronic neutropenia and rheumatoid artritis-like symptoms in a child. Pediatr Dev Pathol 2001;4:94-9.
7. Starkebaum G. Leukemia of large granular lymphocytes and rheumatoid artritis. Am J Med 2000;108:744-5.
8. Kwong YL, Lam CC, Chan TM. Posttransplantation lymphoproliferative disease of natural killer cell lineage: A clinicopathological and molecular analysis. Br J Haematol 2000;110:197-202.
9. Wilkinson AH, Smith JL, Hunsicker LG, et al. Increased frequency of posttransplant lymphomas in patients treated with cyclosporine, azothiopurine and prednisone. Transplantation 1989;47:293.
10. Penn I, Porat G. Central nervous system lymphomas in organ allograft recipients. Transplantation 1995; 59:240.
11. Hunt RJ, Thomas JA, Burke M. Epstein-Barr virus associated Burkitt lymphoma in a heart transplant recipient. Transplantation 1996;62:869.
12. Perzova RN, Loughran TP, Dube S, et al. Lack of BLV and PTLV DNA sequences in the majority of patients with large granular lymphocyte leukemia. Br J Haematol 2000;109:64-70.
13. Pawson R, Schulz TF, Matutes E, et al. The human T-cell lymphotropic viruses types I/II are not involved in T-prolymphocytic leukemia and large granular lymphocytic leukemia. Leukemia 1997;11:1305-11.
14. Chan WC, Link S, Mawle A, et al. Heterogeneity of large granular lymphocyte proliferations-delineation of two major subtypes with distinct origins, immunophenotypes, functional and clinical characteristics. Blood 1986;68:1142.
15. Melenhorst JJ, Brummendorf TH, Kirby M, et al. CD8 (+) T-cells in large granular lymphocyte leukemia are not defective in activation and replication-related apoptosis. Leuk Res 2001;25:699-708.
16. Lamy T, Loughran TP Jr. Current concepts: Large granular lymphocyte leukemia. Blood Rev 1999; 13:230-40.
17. Hamidou M, Lamy T. Large granular lymphocyte proliferations. Clinical and pathogenic aspects. Rev Med Interne 2001;22:452-9.
18. Lamy T, Loughran TP. Large granular lymphocyte leukemia. Cancer Control 1998;5:25-33.
19. Saitoh T, Karasawa M, Sakuraya M, et al. Improvement of extrathymic T-cell type of large granular lymphocyte (LGL) leukemia by cyclosporin-A: The serum level of Fas ligand is a marker of LGL leukemia activity. Eur J Haematol 2000;65:272-5.
20. Loughran TP Jr, Abbott L, Gentile TC, et al. Absence of human herpes virus-8 DNA sequences in large granular lymphocyte (LGL) leukemia. Leuk Lymphoma

1997;26:177-80.

21. Pawson R, Schulz TF, Matutes E, et al. The human T-cell lymphotropic viruses types I/II are not involved in T-prolymphocytic leukemia and large granular lymphocytic leukemia. Leukemia 1997;11:1305-11.
22. Pellenz M, Zambello R, Sementazo G, et al. Detection of Epstein-Barr virus by PCR analyses in lymphopriliferative disease of granular lymphocytes. Leuk Lymphoma 1996;23:371-4.
23. Boehrer S, Hinz T, Schui D, et al. T-large granular lymphocyte leukemia with natural killer cell-like cytotoxicity and expression of two different alpha and beta T-cell receptor chains. Br J Haematol 2001; 112:201-3.
24. Hoffmann JJ, Breed WP, Ziekenhuis C. Two patients with chronic lymphocytosis of large granular lymphocytes; benign or premalignant. Ned Tijdschr Geneeskd 2000;144:1323-7.

Address for Correspondence:

Orhan TÜRKEN, MD

Department of Hematology and Oncology
GATA Haydarpaşa Training Hospital
Çamlıca Hospital,
Acıbadem, İstanbul, TURKEY