Diagnosis of large granular lymphocytic leukemia in a patient previously treated for acute myeloblastic leukemia

Sinem Civriz Bozdag,1 Sinem Namdaroglu,1 Omur Kayikci,1 Gulsa Kaygusuz,2 H serif Demiriz,1 Murat Cinarsoy,1 Emre Tekgunduz,1 Fevzi Altuntas1
1Ankara Oncology Education and Research Hospital, Hematology and Stem Cell Transplantation Clinic, Ankara; 2Pathology Department, Ankara University School of Medicine, Ankara, Turkey

Abstract
Large granular lymphocytic (LGL) leukemia is a lymphoproliferative disease characterized by the clonal expansion of cytotoxic T or natural killer cells. We report on a patient diagnosed with T-cell LGL leukemia two years after the achievement of hematologic remission for acute myeloblastic leukemia.

Introduction
Large granular lymphocytic (LGL) leukemia is a lymphoproliferative disease characterized by clonal expansion of cytotoxic T or natural killer (NK) cells. One-third of patients are asymptomatic, while the remaining two-thirds have symptoms related to neutropenia, anemia or autoimmune diseases such as rheumatoid arthritis.1,3

Although, previously, higher numbers of large granular lymphocytes were required for diagnosis, the currently accepted criteria include patients with LGL counts of more than 0.5×10⁹/L for at least six months.4,5 T-cell LGL leukemia is an indolent disease, whereas NK-cell LGL leukemia mostly demonstrates an aggressive course.6,7

Case Report
We report a patient diagnosed with T-cell LGL leukemia two years after the achievement of hematologic remission for acute myeloblastic leukemia (AML). A 57-year old male patient presented with weakness and fever. Physical examination showed fever of 38°C, pallor and hepatosplenomegaly. Complete blood count (CBC) showed; white blood cell (WBC) count 45×10⁹/L, absolute neutrophil count (ANC) 0.014×10⁹/L, hemoglobin (Hb) 9 gr/dL, platelets (Plt) 43×10⁹/L. Peripheral blood smear showed 90% of the cells were myeloblasts and thrombocyte counts were consistent with CBC. Flow cytometry analysis revealed 93% blasts with the following antigens: MPO+, HLA DR-, CD33+, CD34+, CD117+, CD64-, CD14-, CD13-, CD 7-. Cytogenetic analysis was 46,XY. He was diagnosed as AML not otherwise specified (NOS). Induction therapy (7+3) was started and at Day 3 of chemotherapy, Klebsiella and Candida crusei were grown in spumut culture. Thorax high-resolution computed tomography revealed peribronchial thickness and ground glass appearance in the lower lobes of both lungs in addition to a 1.5×1 cm diameter nodule that was detected in the right upper lobe. Serum galactomannan levels were in the normal range. Abdominal ultrasonography showed hepatomegaly and hypodens nodular areas (largest 2.5×3.5 cm) in spleen. Bone marrow aspiration biopsy was performed on Day 28 of chemotherapy and the patient was found to be in hematologic remission. Despite antifungal treatment, fever and nodules in spleen persisted so splenectomy was performed for differential diagnosis. Pathological examination of spleen revealed congestion but no fungal infection.

During follow up, fever was under control and consolidation therapy with high-dose ARA-C (6 g/m² Days 1,3 and 5) was started. The third consolidation treatment was complicated with Wernicke encephalopathy and treated with intravenous thiamine supplementation. This therapy led to a partial recovery but the patient could not proceed with subsequent consolidation treatment due to poor performance status. Paraparesia continued and physical therapy was scheduled; this improved the patient’s motor weakness. At the sixteenth month of his follow up in remission, leukocytosis was observed in CBC without any systemic complaints except weakness in both legs. CBC results were: WBC 16×10⁹/L, ANC 4.5×10⁹/L, lymphocytes 11×10⁹/L, Plt 226×10⁹/L, and Hb 14 gr/dL. Peripheral blood smear was consistent with CBC and 60% of the leukocytes were made up of large granular lymphocytes. In flow cytometry analysis of peripheral blood, 57% of leukocytes were lymphocytes and 89% of lymphocytes were T cells. Seventy-two percent of T cells were LGL; 98% of them expressed TCR alpha beta and 2% of them expressed TCR gama delta. Clonality of T cells were also confirmed by multiplex PCR analysis. Chest-abdomen-pelvis tomography revealed no lymphadenopathy. Rheumatoid factor and antinuclear antibody (ANA) levels were found to be negati- ve. As the patient did not have any complaints due to LGL counts or any kind of autoimmune disease, he was followed up without treatment. At the 26th month of follow up, he is still in hematologic remission for AML diagnosis. His blood counts are stable and he still does not have any complaints except weakness in both his legs.

Discussion
Large granular lymphocytes are the cells which undergo apoptosis after contact with an infected cell. These cells are either CD3- NK or CD3+ T cells.5 The LGL clone has been shown to manifest in the context of an initially polyclonal immune response or an autoimmune process.4 The majority (80-90%) of patients with T-LGL leukemia show a CD3+CD8+CD57+CD56–CD28–, TCR- phenotype.2

Clonality of T LGL is mostly demonstrated by TCR- PCR analyses. Flow cytometric T-cell receptor V repertoire analysis can also be used for diagnosis of a clonal T-cell population.9,10 One of the largest series published from France revealed that 51% of LGL leukemia patients were diagnosed with hyperlymphocytosis.5 Neutropenia was found to be more frequent than anemia and thrombocytopenia. Severe neutropenia was associated with recurrent infections.11 Our patient was not neutro- penic or anemic when he was diagnosed but his lymphocyte count was more than 10×10⁹/L. Rheumatoid factor and antinuclear antibodies can be detected in patients with LGL leukemia and autoimmune diseases such as rheumatoid arthritis. Rheumatoid factor and ANA levels were normal in our patient and there were no
symptoms that could be related to any autoimmune disease. Splenomegaly ranged from 19% to 50% in different series.\(^4,12\) Splenectomy was reported to be a valid therapeutic option in cases of T-LGL leukemia with splenomegaly and refractory cytopenia.\(^4\) Interestingly, in our patient, increase in the LGL count appeared approximately two years after splenectomy.

Reactive T-cell lymphoproliferation can be associated with malignancies. There are case reports of B-cell chronic lymphocytic leukemia, splenic lymphoma with villous lymphocytes, hairy cell leukemia, monoclonal gammopathy of undetermined significance (MGUS), and multiple myeloma associated with LGL leukemia.\(^3,15\) In a French cohort, myelodysplasia and B-cell lymphoid neoplasms were diagnosed in 17% and 5% of patients, respectively. Only 2 patients were diagnosed as AML in this study. Autoreactive T cells were held responsible for the pathogenesis of T-LGL and association with aplastic anemia or myelodysplastic syndrome. But the exact pathogenesis of other hematologic malignancies and T-LGL must still be explained. All these neoplasms were reported to present from six to 16 years before the diagnosis of LGL proliferation.\(^5\) In our patient, LGL proliferation progressed in the second year of AML diagnosis and despite splenectomy.

The majority of LGL leukemia patients are symptomatic at the time of presentation. In a French cohort, 44% of the patients required treatment during follow-up.\(^5\) But since our patient was asymptomatic except for weakness in his legs, for the moment we have not started any therapy.

## Conclusions

In conclusion, we report a patient diagnosed as LGL leukemia two years after the achievement of hematologic remission of AML and splenectomy. Concurrent AML and LGL leukemia diagnosis is extremely rare and our case is also interesting because of the occurrence of LGL leukemia after splenectomy which is a modality used for its treatment.

## References

1. Liu X, Loughran TP Jr. The spectrum of large granular lymphocyte leukemia and Felty’s syndrome. Curr Opin Hematol 2011;18:254-9.
2. Sokol L, Loughran TP Jr. Large granular lymphocyte leukemia. Oncologist 2006;11:263-73.
3. Lamy T, Loughran TP. Clinical features of large granular lymphocyte leukemia. Semin Hematol 2003;40:185-95.
4. Lamy T, Loughran TP Jr. How I treat LGL leukemia. Blood 2011;117:2764-74.
5. Bareau B, Rey J, Hamidou M, et al. Analysis of a French cohort of patients with large granular lymphocyte leukemia: a report on 229 cases. Haematologica 2010;95:1534-41.
6. Pandolfi F, Loughran TP Jr., Starkebaum G, et al. Clinical course and prognosis of the lymphoproliferative disease of granular lymphocytes: a multicenter study. Cancer 1990;65:341-8.
7. Suzuki R, Suzumiya J, Nakamura S, et al. Aggressive natural killer-cell leukemia revisited: large granular lymphocyte leukemia of cytotoxic NK cells. Leukemia 2004;18:763-70.
8. Watters RJ, Liu X, Loughran TP Jr. T-cell and natural killer-cell large granular lymphocyte leukemia neoplasias. Leuk Lymphoma 2011;52:2217-25.
9. Zhang D, Loughran TP Jr. Large granular lymphocytic leukemia: molecular pathogenesis, clinical manifestations, and treatment. ASH Education Book 2012;1:652-9.
10. Hsieh YC, Chang ST, Huang WT, et al. A comparative study of flow cytometric T cell receptor V\(\beta\) repertoire and T cell receptor gene rearrangement in the diagnosis of large granular lymphocytic lymphoproliferation. Int J Lab Hematol 2013;35:501-9.
11. Loughran TP Jr. Clonal diseases of large granular lymphocytes. Blood 1993;82:1-14.
12. Subbiah V, Viny AD, Rosenblatt S, et al. Outcomes of splenectomy in T-cell large granular lymphocyte leukemia with splenomegaly and cytopenia. Exp Hematol 2008;36:1078-83.
13. Hanada T, Ishida T, Kojima H, Tsuchiya T. Granular lymphocyte leukemia in association with multiple myeloma. Br J Haematol 1992;80:127-9.
14. Papadaki T, Stamopoulos K, Kosmas C, et al. Clonal T-large granular lymphocyte proliferations associated with clonal B cell lymphoproliferative disorders. Report of eight cases. Leukemia 2002;16:2167-9.
15. Lesveve JF, Feugier P, Lamy T. Association of B-chronic lymphocytic leukemia and T-large granular lymphocyte leukemia. Clin Lab Haematol 2000;22:121-2.