A Case of Concomitant T-Cell Large Granular Lymphocyte Leukemia and Plasma Cell Myeloma

Ubaid Nawaz, MD[1]
Said Baidas, MD[2]
Edward Jones, MD[3]

[1]*Vince Lombardi Cancer Clinic, Aurora Healthcare, Greenbay, Wisconsin*
[2]*Department of Hematology and Oncology, MD Anderson Cancer Center Orlando, Orlando, Florida*
[3]*Department of Pathology, Parrish Medical Center, Titusville, Florida*

A 71-year-old man presented with asymptomatic anemia. He was found to have a hemoglobin of 8.7 g/dL and a white blood cell count of 10,500/mm^3. Absolute lymphocyte count was elevated at 8,900/mm^3. Absolute neutrophil count was decreased at 800/mm^3. Platelet count was normal at 196,000/mm^3. Peripheral smear review revealed lymphocytosis with atypical small lymphocytes containing cytoplasmic granules (Figure 1). Serum protein electrophoresis showed a monoclonal spike of 1.7 g/dL. Immunofixation identified a monoclonal immunoglobulin (Ig)G kappa band. Serum kappa free light chains were increased at 97.2 mg/dL, with an abnormal kappa-lambda ratio of 110. IgG was elevated at 2,874 mg/dL and the IgA and IgM were decreased at 91 mg/dL and 45 mg/dL, respectively. A skeletal survey was negative for lytic lesions. A computed tomography scan of the chest, abdomen, and pelvis was unremarkable. HIV and human T-lymphotropic virus (HTLV) 1/2 testing were negative.

The bone marrow biopsy showed a hypercellular marrow, with an increase in both plasma cells (15–20%) and small T lymphocytes (30–40%). The plasma cells had a diffuse distribution, with a formation of numerous aggregates (Figure 2). By flow cytometry, the plasma cells exhibited kappa light chain restriction, which, in addition to the above mentioned serologic findings, is diagnostic of plasma cell myeloma.

The abnormal lymphocyte population in both the bone marrow and peripheral blood displayed increased side scatter and expression of CD3, CD8, CD16, and CD57, with aberrant, diminished expression of CD5 and CD7 (Figure 3). The abnormal lymphocytes lacked expression of CD4, CD25, and CD56. Additionally, a dominant population (82%) expressed the $V_\beta 20$ T-cell receptor subtype. The abnormal lymphocytes in the bone marrow were positive for CD3 and TIA-1 expression by immunohistochemistry (Figure 4). These findings are consistent with T-cell large granular lymphocytic (T-LGL) leukemia.

Address correspondence to:
Ubaid Nawaz, MD, Hematology and Oncology, Vince Lombardi Cancer Clinic, Aurora Health Care, 2845 Greenbriar Rd, Green Bay, WI 54308; Phone: 920-288-4180; E-mail: ubaid.nawaz@aurora.org.

Discussion

To the best of our knowledge, this is the first reported case of concomitant T-LGL leukemia and plasma cell myeloma. Although it has been reported that the incidence of B-cell dyscrasias is higher in patients with

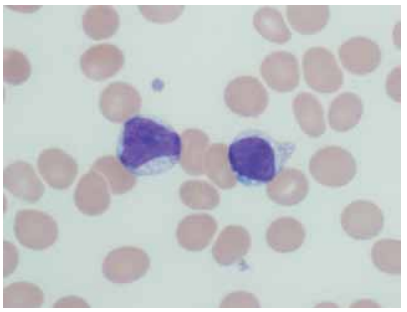

Figure 1. Peripheral blood with large granular lymphocytes.

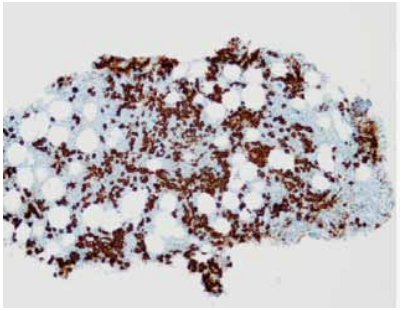

Figure 2. Bone marrow biopsy, CD138 immunohistochemistry stain.

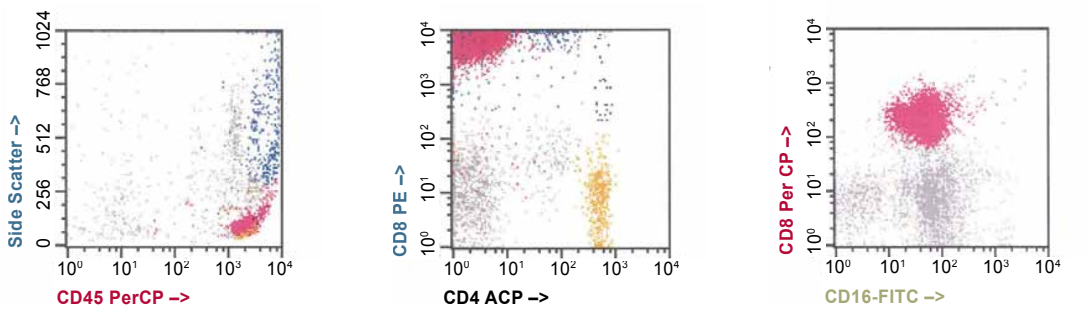

Figure 3. Select flow cytometric histograms of peripheral blood demonstrating lymphocytes with increased side scatter and expression of CD8/CD16.

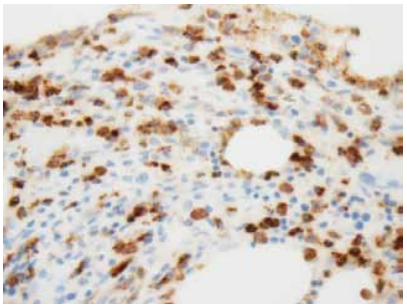

Figure 4. Bone marrow biopsy, TIA-1 immunohistochemistry stain.

T-LGL leukemia, and that the monoclonal gammopathy of undetermined significance (MGUS)[1] is one of the most common concomitant B-cell dyscrasias, plasma cell myeloma has not been reported to occur concomitantly with T-LGL leukemia. LGL leukemia represents a spectrum of disorders, including T-cell and natural killer (NK)-cell leukemia; typically, there is an indolent course and a favorable prognosis. Less commonly, there can be an aggressive course with a poor outcome. T-LGL leukemia is associated with an increased incidence of Epstein-Barr virus and human T-lymphotropic virus type 1 (HTLV1) infections. Cytopenias, autoimmune conditions like rheumatoid arthritis, and recurrent infections are commonly associated with T-LGL leukemia.[2] Patients with aggressive variants of T-LGL leukemia may have B symptoms, lymphadenopathy, and a rapidly worsening clinical course that distinguishes it from the indolent variants. Treatment for indolent LGL leukemia typically involves immunosuppression with methotrexate, cyclosporine, steroids, and cyclophosphamide (either as a single agent or in combination). For aggressive LGL leukemia, treatment with chemotherapy regimens similar to acute lymphoblastic leukemia regimens are used, followed by evaluation for hematopoietic stem cell transplant. In this patient, we recommended treatment for the T-LGL leukemia, as it was believed to be the main cause of the patient's anemia and neutropenia, and observation for the plasma cell myeloma. The patient was started on methotrexate and prednisone.

References

1. Viny AD, Lichtin A, Pohlman B, Loughran T, Maciejewski J. Chronic B-cell dyscrasias are an important clinical feature of T-LGL leukemia. *Leuk Lymphoma*. 2008;49:932-938.
2. Alekshun TJ, Sokol L. Diseases of large granular lymphocytes. *Cancer Control*. 2007;2:141-150.

Review

A Case of Concomitant T-Cell Large Granular Lymphocytic Leukemia and Plasma Cell Myeloma

H. Elizabeth Broome, MD, and
Huan-You Wang, MD, PhD

Moores UCSD Cancer Center and the Division of Clinical Pathology, Department of Pathology, University of California, San Diego, La Jolla, California

T-cell large granular lymphocytic (T-LGL) leukemia is a subtype of LGL leukemia defined by the World Health Organization (WHO) classification system as a persistent (>6 months) increase in blood LGL ($2–20 \times 10^9$/L) without a clearly identified cause.[1] These diagnostic criteria are vague and controversial since 25–30% of patients with a clonal T-LGL population causing disease do not have an increase in the absolute T-LGL count.[2] Also, the presence of clonal T-LGL may not always correlate with clinical symptoms. The term T-cell clonopathy of undetermined significance (TCUS) was coined to emphasize that there is a clinical spectrum of clonal T-LGL proliferations from TCUS to disease-causing T-LGL leukemia.[3] Many investigators of T-LGL leukemia use diagnostic criteria that do not depend on an absolute increase in the T-LGL count or a waiting period. Instead, these investigators use the criteria of a detectable clone of T-LGL in patients with symptoms or cytopenias commonly found in T-LGL leukemia. These symptoms include those associated with concomitant autoimmune diseases, such as rheumatoid arthritis or cytopenias without other explanation.[2]

The association of T-LGL leukemia with autoimmune disorders is well documented, but recent reports also document the association of T-LGL leukemia with B-cell lymphoproliferative disorders (B-LPD) and, rarely, myeloid neoplasms.[2,3] Most of the associated B-LPD are subclinical, including monoclonal gammopathies of undetermined significance (MGUS)[4] or monoclonal B-cell lymphocytosis.[5] However, T-LGL does occur in association with symptomatic and progressive cases of B-LPD, including non-Hodgkin lymphoma and B-cell chronic lymphocytic leukemia (CLL). MGUS is defined by the presence of a paraprotein without other evidence of disease. Monoclonal B-cell lymphocytosis is defined by the presence of monoclonal B cells in the blood of apparently healthy individuals with normal blood counts and no other evidence of lymphoma. The case reported by Nawaz and colleagues,[6] a recent publication authored by the reviewers,[7] plus other reports[2,3] further document the association of T-LGL leukemia with B-LPD, confirming that the spectrum of associated conditions includes plasma cell myeloma.

Investigating the intriguing association of T-LGL leukemia with autoimmune disorders or B-LPD may lead to better understanding of the pathophysiology of these diseases. The associations of T-LGL leukemia with autoimmune disorders versus B-LPD appear to be largely independent because about one third of patients with T-LGL leukemia have B-LPD, while another one-third of patients with T-LGL leukemia have rheumatoid arthritis (RA) or other autoimmune disease.[2,8] Only 2 of 16 T-LGL leukemia cases associated with B-LPD had autoimmune disease. Although these populations have little overlap, both B-LPD and autoimmune diseases may contribute to the development of T-LGL leukemia through a related mechanism, possibly chronic immune stimulation. Many investigators have suspected that chronic immune stimulation contributes to the development of T-LGL leukemia. The main evidence for this hypothesis is the association of T-LGL leukemia with autoimmune disease and the characteristic terminal effector memory T-cell phenotype of T-LGL leukemia.

RA patients are the most well-defined autoimmune disease population with an increased risk of developing T-LGL leukemia. One report estimates that 0.6% of all RA patients develop T-LGL leukemia.[9] Most, but not all of the T-LGL proliferations associated with RA are clonal by Southern blot with probes to the TCR beta chain. Nonclonal, oligo-clonal, or even clonal T-LGL proliferations occur in many reactive conditions, including viral infections and postmarrow transplant.[10] Therefore, only certain, possibly more chronic, causes of T-LGL proliferations seem to contribute to the development of clinically significant T-LGL leukemia. One hypothesis about the association of T-LGL proliferations and autoimmune disease is that the T-LGL proliferations result from a failure of apoptosis of self-reactive T cells, similar to an RA-like disease in mice that is associated with FAS or FAS-ligand gene mutations (lpr/lpr mice). Activated lymphocytes in these mutant mice accumulate due to resistance to physiologic FAS-mediated apoptosis. There is evidence that T-LGL proliferations in humans are resistant to FAS-mediated apoptosis, but no mutations in FAS or FAS-ligand have been identified so far.

Address correspondence to:
H. Elizabeth Broome, MD, Moores UCSD Cancer Center, Division of Clinical Pathology, Department of Pathology, University of California, San Diego, California 92093-0987; Phone 858-822-6279; Email: ebroome@ucsd.edu.

Although there is no evidence that T-LGL leukemia in humans is associated with FAS or FAS-ligand mutations, T-LGL leukemia occurs more frequently in humans with specific polymorphisms of MHC class I–related chain A (MICA), a ligand for the NKG2D co-stimulatory receptor found on NK cells, gamma/delta T cells, and T-LGL.[11] Engagement of NKG2D by surface-expressed ligands including MICA enhances the cytolytic activity and cytokine production of T cells. Sixty-eight percent of T-LGL leukemia patients had a MICA allele that was present in only 29% of control individuals. Homozygosity for this allele was present in 39% of T-LGL leukemia patients compared to 8% of controls. Normally, MICA is present only on gastrointestinal epithelium, endothelial cells, and fibroblasts, but stress induces MICA expression on many cells. Inducing stressors include viral infections, bacterial infections, and heat shock. Also, MICA is expressed on many tumor cells, including hematopoietic neoplasms, such as myeloma and CLL.

Of particular relevance to the current case report, plasma cells in MGUS express MICA, usually at higher levels than in myeloma,[12] and the MICA on these neoplastic plasma cells can activate NKG2D expressing cytolytic T cells. One hypothesis is that as MGUS progresses to myeloma, the neoplastic plasma cells may lose MICA expression to avoid immune surveillance. Another immune avoidant strategy, possibly used by CLL, is to secrete soluble NKG2D ligands, such as MICA. These soluble ligands may serve as decoys to inhibit cytolytic T-cell function. Evidence that CLL may use this "decoy" strategy is that serum levels of soluble NKG2D ligands such as MICA are increased in CLL and correlate inversely with outcome.[13]

One question about the significance of MICA polymorphisms and T-LGL leukemia is if MICA is so broadly expressed on hematopoietic malignancies, including acute leukemias and chronic myelogenous leukemia, then why are T-LGL leukemias more commonly associated with certain B-LPD, such as subclinical B-cell lymphocytosis proliferations and MGUS? Possible explanations may involve prevalence and chronicity. B-LPDs are much more common than other hematopoietic neoplasms, and they are very chronic, often going undetected for decades. Many T-LGL leukemias have associated B-LPDs that are detectable only by very sensitive screening, such as serum free light chain measurements or sensitive flow cytometry techniques.[5]

If B-LPDs and autoimmune disorders contribute to the development of T-LGL leukemia through a similar chronic immune stimulation mechanism, possibly involving MICA, then what are the implications for therapy? Stimulating other aspects of the immune system to target the subclinical B-LPD with drugs such as lenalidomide (Revlimid, Celgene)[14] or pamidronate[12] may effectively treat the T-LGL leukemia. Alternatively, blocking the NKG2D receptor on the T-LGL leukemia may decrease the chronic activation of the T-LGL leukemia cells. However, if the T-LGL leukemia is contributing to the suppression of the B-LPD, then blocking that receptor may allow the B-LPD to progress.

Besides therapeutic implications, these recent findings raise further questions worth investigating, including: What proportion of T-LGL leukemia patients have detectable B-LPD using the most sensitive techniques, such as immunoglobulin gene rearrangements by polymerase chain reaction? Are there other immunogenetic changes associated with T-LGL leukemia aside from the skewed MICA polymorphism? How does the implicated MICA allele contribute to the development of T-LGL leukemia? The rapidly progressing research in this field shows promise of imminent, therapeutically-significant developments.

References

1. Chan WC, Foucar K, Morice WG, Catovsky D. T-cell large granular lymphocytic leukemia. In: Swerdlow S, Campo E, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon, France: IARC Press; 2008:272-275.
2. 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;95:1534-1541.
3. Dhodapkar MV, Li CY, Lust JA, Tefferi A, Phyliky RL. Clinical spectrum of clonal proliferations of T-large granular lymphocytes: a T-cell clonopathy of undetermined significance? *Blood.* 1994;84:1620-1627.
4. Viny AD, Lichtin A, Pohlman B, Loughran T, Maciejewski J. Chronic B-cell dyscrasias are an important clinical feature of T-LGL leukemia. *Leuk Lymphoma.* 2008;49:932-938.
5. Howard MT, Bejanyan N, Maciejewski JP, Hsi ED. T/NK large granular lymphocyte leukemia and coexisting monoclonal B-cell lymphocytosis-like proliferations. An unrecognized and frequent association. *Am J Clin Pathol.* 2010;133:936-941.
6. Nawaz U, Baidas S, Jones E. A case of concomitant T-cell large granular lymphocyte leukemia and plasma cell myeloma. *Clin Adv Hematol Oncol.* 2011;9:956-957.
7. Xu X, Broome HE, Rashidi HH, South ST, Dell'Aquila ML, Wang HY. CD20dim-positive T-cell large granular lymphocytic leukemia in a patient with concurrent hairy cell leukemia and plasma cell myeloma. *Int J Clin Exp Pathol.* 2010;3:798-807.
8. Wlodarski MW, Schade AE, Maciejewski JP. T-large granular lymphocyte leukemia: current molecular concepts. *Hematology.* 2006;11:245-256.
9. Saway PA, Prasthofer EF, Barton JC. Prevalence of granular lymphocyte proliferation in patients with rheumatoid arthritis and neutropenia. *Am J Med.* 1989;86:303-307.
10. Sabnani I, Zucker MJ, Tsang P, Palekar S. Clonal T-large granular lymphocyte proliferation in solid organ transplant recipients. *Transplant Proc.* 2006;38:3437-3340.
11. Viny AD, Clemente MJ, Jasek M, et al. MICA polymorphism identified by whole genome array associated with NKG2D-mediated cytotoxicity in T-cell large granular lymphocyte leukemia. *Haematologica.* 2010;95:1713-1721.
12. Girlanda S, Fortis C, Belloni D, et al. MICA expressed by multiple myeloma and monoclonal gammopathy of undetermined significance plasma cells costimulates pamidronate-activated gammadelta lymphocytes. *Cancer Res.* 2005;65:7502-7508.
13. Nuckel H, Switala M, Sellmann L, et al. The prognostic significance of soluble NKG2D ligands in B-cell chronic lymphocytic leukemia. *Leukemia.* 24:1152-1159.
14. Merchionne F, Perosa F, Dammacco F. New therapies in multiple myeloma. *Clin Exp Med.* 2007;7:83-97.