T-Cell Large Granular Leukemia and Related Proliferations

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Abstract

Session 9 of the 2005 Society for Hematopathology/European Association for Haematopathology Workshop focused on large granular lymphocyte (LGL) leukemias and related disorders. T-cell LGL (T-LGL) leukemias, discussed herein, account for 2% to 3% of cases of small lymphocytic leukemia. T-LGL diseases cover a heterogeneous spectrum of disorders that include reactive conditions, typically associated with autoimmune disease, to outright leukemia. These disorders are found in older people, with an average age at initial examination of approximately 60 years and a median survival of more than 10 years in T-LGL leukemia. Systemic symptoms and neutropenia are common at initial examination. Lymphocytosis, composed of small mature lymphocytes with increased cytoplasm, is common. The spleen and bone marrow are involved in T-LGL leukemia, although morphologic findings may be subtle. The immunophenotype is typically that of CD3+/CD8+ cytotoxic T cells. Some cases may be due to chronic immune stimulation, with subsequent clonal escape and proliferation of a neoplastic population of lymphocytes.

In session 9 of the Society for Hematopathology/European Association for Haematopathology Workshop, disorders of large granular lymphocytes (LGLs) were addressed. Cases with a natural killer cell immunophenotype are discussed in detail by Hasserjian and Harris in this issue of the Journal. T-cell LGL disorders are the focus of the present article.

Among the T-cell malignancies, T-cell LGL (T-LGL) diseases are not uncommon, and leukemias of LGL, originally defined by McKenna et al. in 1977, account for 2% to 3% of all cases of small lymphocytic leukemia. T-LGL diseases cover a heterogeneous spectrum of disorders that includes reactive conditions, typically associated with autoimmune disease, and overt T-LGL leukemia. Despite this heterogeneity, T-LGL disorders have a relatively well-defined clinical spectrum and pathologic features that help define them. A diagnostic algorithm for T-LGL disorders is shown in Figure 1.

Throughout this article, a distinction is made between T-LGL leukemia, a well-defined neoplasm of CD8+ T-lymphocytes, and T-LGL disease. T-LGL disease is a reactive condition associated with a proliferation of “normal” CD8+ cytotoxic T lymphocytes, usually in association with autoimmune disease, and may be a precursor of T-LGL leukemia in some circumstances. Nonleukemic T-LGL proliferations may be transient or chronic. There are undoubtedly individual borderline cases that fall in the zone between reactive and leukemic T-LGL disorders. Some authors have gone as far as to suggest that there is a “T-cell clonopathy of undetermined significance” analogous to monoclonal gammopathy of undetermined significance.
Clinical Features

T-cell LGL disease and leukemia are found in older people, with an average age at initial examination of approximately 60 years, although it has been reported in all age groups, including children. Men and women are equally affected. The average time from appearance of symptoms to diagnosis of T-LGL leukemia is 37 months. Median survival of more than 10 years is typical for patients with T-LGL leukemia.

Typical clinical symptoms and signs of patients with T-LGL leukemia include fever, recurrent bacterial infections, fatigue, and weight loss. Mild to moderate splenomegaly is seen in many patients (20%-60%), and hepatomegaly is less common (<20%). Neutropenia, often severe, is the most uniform feature and is present in 60% to 85% of symptomatic patients at initial examination. Lymphadenopathy is rare. Other associations that occur rarely are neuropathy, solid tumors, endocrinopathy, and monoclonal gammopathy of undetermined significance. Despite this impressive array of symptoms, up to one third of patients are diagnosed based on the detection of asymptomatic cytopenias.

One of the primary findings in T-LGL leukemia is the presence of lymphocytosis. It is typically in the range of 2,000 to 20,000/µL (2-20 × 10⁹/L; median, 4,000-8,000/µL [4-8 × 10⁹/L]) at initial diagnosis. In contrast, the normal number of LGLs in peripheral blood (PB) is 0.1 to 0.3 × 10⁹/L. For diagnostic purposes, the lymphocytosis of T-LGL leukemia should be sustained for at least 6 months. In cases of obvious leukemia (eg, extremely high WBC count), this criterion is not necessary, and other diagnostic methods, as outlined subsequently, may also make this standard less necessary. Serologic abnormalities are quite frequent findings in patients with T-LGL leukemia. These findings are summarized in Table 1.

Benign, reactive increases in LGLs are seen in association with a variety of causes, including splenectomy, HIV infection, other viral infections, allogeneic stem cell transplantation, and solid organ transplantation. Furthermore, persistent clonal expansions of CD8+ T-cell subsets are seen in some elderly people, and these do not develop into T-LGL leukemia.

In addition, autoimmune diseases are associated with T-cell LGL disease and leukemia. Reported autoimmune disorders associated with T-LGL leukemia include rheumatoid arthritis (25%), Felty syndrome (up to 40%), Evans syndrome, Sjögren syndrome, Hashimoto thyroiditis, autoimmune polyglandular syndrome, Graves disease, Cushing syndrome, hyperparathyroidism, multiple sclerosis, ulcerative colitis, recurrent uveitis and psoriasis.

Rare cases of T-LGL leukemia have been seen after renal and liver transplantation. In addition, T-LGL leukemia has been reported after allogeneic bone marrow (BM) transplantation. Surprisingly, these leukemias were proven to be of donor origin; Epstein-Barr virus (EBV) infection was not found in any of the cases, but it was suggested that the leukemia may have been driven by antigenic response to cytomegalovirus infection or, possibly, graft-vs-host disease.

A variety of therapies are available for patients with T-LGL leukemia. Because of its relatively indolent clinical behavior, observation is an appropriate therapy. Other options include granulocyte colony-stimulating factor (for cytopenias), steroids, low-dose methotrexate, cyclophosphamide, cyclosporine, purine analogs (pentostatin, fludarabine), and alemtuzumab (Campath-1H). In many cases, the goal of therapy is improvement of neutropenia and reduction of infections.

Hematologic Manifestations

A wide range of hematologic manifestations are seen in association with T-LGL disease and leukemia. Cytopenias in patients with T-LGL leukemia suggest that the clonal lymphocytes recognize lineage-committed hematopoietic progenitor cells in the BM. As mentioned, neutropenia is frequently seen; adult cyclic neutropenia is a rare condition, and almost all cases are associated with T-LGL
Increased numbers of infections due to bacteria are seen and are thought to be related to decreased numbers of neutrophils and/or impaired neutrophil function. In addition, chronic anemia is seen in approximately 50% of patients. It is often multifactorial but may have a prominent component of autoimmune hemolytic anemia. Pure red cell aplasia has been reported in 8% to 19% of patients with T-LGL leukemia, and T-LGL leukemia is probably the most common cause of pure red cell aplasia. Parvoviral infection can induce pure red cell aplasia in patients with T-LGL leukemia. Thrombocytopenia occurs in approximately 20% of patients. Immune thrombocytopenic purpura also has been reported with increased frequency in patients with increased T-LGLs. This may not be a direct effect, but rather an association with the autoimmune disease seen in the patients. Aplastic anemia and myelodysplastic syndrome (MDS) have been reported in patients with T-cell LGL disease and leukemia. In comparison with cases of T-LGL leukemia alone and MDS alone, patients with combined T-LGL leukemia/MDS are significantly older (median age, 64.4 years), have different PB T-LGL counts (0.4 × 10^9/L vs 1.36 × 10^9/L for T-LGL leukemia and 0.11 × 10^9/L for MDS), and cytopenias respond to cyclosporine. These authors suggest that, in some cases, the MDS may be causally linked with the T-LGL proliferations arising in a setting of abnormal MDS-related antigens.

**PB and Histologic Findings**

The PB appearance of T-LGL disease is characteristic but may be underappreciated when the absolute lymphocyte count is low. T-LGLs are characterized by intermediate to large size (15-18 µm) with increased amounts of pale cytoplasm. The T-LGL nucleus is typically round with condensed, mature chromatin, although the nuclear chromatin may appear more open or “ropey.” Within the cytoplasm are variable numbers of randomly distributed azurophilic granules. When numerous, LGLs are easy to identify as a distinct population. In normal circumstances, LGLs make up 5% to 15% of PB lymphocytes. Associated findings, as mentioned, include cytopenias, especially decreased numbers of neutrophils. Distinguishing a reactive or benign increase of T-LGLs from T-LGL leukemia is usually not possible based on morphologic features alone.

BM involvement by T-LGL disease is often subtle and difficult to identify, even when apparent in the PB. In BM aspirate smears, individual or small clusters of T-LGLs may be identified, although they are often few. Furthermore, they are difficult to identify as a distinct population because of their morphologic similarity to granulocytic or monocytic precursors. Careful attention to nuclear morphologic features (eg, dense, mature chromatin) may help distinguish them from myeloid precursors. The BM infiltration by T-LGL diseases and leukemia is often composed of subtle interstitial infiltration of individual lymphocytes or small clusters. In addition,
the lymphocytes may be present in an intravascular or linear pattern, with individual cells or small lines within BM vascular elements. In both of these types of BM involvement, immunohistochemical analysis is important to identify the pattern and degree of involvement (see “Immunophenotype”). In more exceptional cases, the infiltrates are more extensive, with larger interstitial infiltrates of small lymphocytes. In H&E-stained sections, the increased amounts of cytoplasm are often less apparent than in BM aspirate or PB smears. Reactive lymphoid aggregates composed of B and T cells are seen in the majority of cases. These may have subtle involvement at the periphery of the nodules by the abnormal T cells, but they are difficult to distinguish from typical reactive lymphoid follicles in the BM.

Splenic involvement by T-LGL proliferations has a relatively characteristic appearance. In most cases, there is mild to moderate enlargement of the spleen. The pattern is typically expansion of the red pulp, with only minimal changes in the white pulp. The red pulp shows increased cellularity, with a large population of small lymphocytes. In well-fixed and prepared sections, the increased amounts of cytoplasm of T-LGL cells may be appreciated. As in other sites, the T-LGLs have small, round nuclei with mature chromatin. Their infiltration in the red pulp includes the splenic sinuses with marked

![Image 2](https://example.com/image1.png)  ![Image 3](https://example.com/image2.png)  ![Image 4](https://example.com/image3.png)  ![Image 5](https://example.com/image4.png)

**Image 2** Bone marrow findings in large granular lymphocyte (LGL) leukemia. A, Bone marrow findings in H&E-stained biopsy sections are often subtle. Individual infiltrating neoplastic lymphocytes are difficult to recognize (×500). Immunohistochemical results for CD8 (B, ×500), T-cell intracellular antigen-1 (C, ×500), and granzyme B (D, ×500) highlight the subtle infiltration of the bone marrow by the T-cell LGL leukemia. These stains also highlight the pattern of sinusoidal infiltration that is not an uncommon finding in LGL leukemia.
distention of the cords. In the white pulp, germinal centers may be present and may be hyperplastic or regressed. The periarteriolar lymphoid sheaths regions are composed predominantly of T lymphocytes. These zones are often infiltrated by the neoplastic lymphocytes of T-LGL leukemia, with subtle expansions in size. However, this infiltration is often difficult to recognize based entirely on morphologic examination and is only apparent by immunohistochemical examination.

As mentioned, lymphadenopathy is a rare finding in patients with T-LGL disorders. Little is written about lymph node involvement in T-LGL leukemia. As with other T-cell leukemias and circulating lymphomas, the sinuses and interfollicular areas of the lymph node are most prominently involved. The process may entirely efface the lymph node. As in other histologic preparations, the lymphocytes are predominantly small and round with mature chromatin. The increased amount of cytoplasm may impart a pale appearance to the infiltrating cells, somewhat similar to the monocytoid B-cell appearance seen in nodal marginal zone lymphomas. Liver involvement is frequent, but liver samples are only rarely examined in T-LGL leukemia. Abnormal lymphocytes are present in the sinuses, singly or in small clusters. There may be subtle expansion of the portal triads by infiltrates of small lymphocytes in small aggregates.
Immunophenotype

The immunophenotypic features are important in diagnosis and the pathobiology of T-LGL disorders. Flow cytometric immunophenotypic analysis (FC) is the most powerful method for diagnosing T-LGL leukemia, by demonstrating an abnormal immunophenotype in the T-LGLs. As mentioned, the normal T-LGL is a CD8+ T cell with the following immunophenotype: CD2+, cyttoplasmic CD3+, CD4–, CD5+, CD7+, CD8+, CD16–, CD56–, αβ T-cell receptor (TCR)+, and γδ TCR−. The neoplastic counterpart, seen in T-LGL leukemia has an abnormal immunophenotype in virtually all cases.

Lundell and colleagues recently showed that 80% of LGL leukemias had abnormal expression of 2 or more pan-T-cell antigens. CD5 and CD7 are most commonly abnormal, with dim or absent expression the most common, although abnormal bright expression may be seen as well. CD57 FITC, CD5 PC5, CD16 FITC, CD8 PE, CD158a FITC, CD158b FITC, and p70/nkb1 FITC, CD158a–R2, CD16 PE, CD158b+ are shown to express CD3 and CD16 in this case, in contrast with normal lymphocytes (red), which do not express CD16 (upper left histogram). The remaining histograms show a uniform lack of expression of CD158a (upper right), CD158b (lower left), and CD158e (lower right). Uniform expression of a single KIR antigen or lack of expression of all KIR antigens is abnormal and is a finding in most LGL leukemias. Case contributed by W. Morice.

Abnormal diminished expression of CD3 or CD2 and other T-cell antigens can also be seen rarely. Expression of natural killer (NK)-related antigens CD16 (~80%) and CD57 (near 100%) is usual in T-LGL leukemia, although their expression is also seen in a small subset of normal, cytotoxic T cells, the “NK-like T cells.” CD57 is thought to define the effector subset of CD8+ T cells. This suggests that the malignant clone can have different immunophenotypic subsets, some with an effector phenotype and others with a memory phenotype.

Although most cases are αβ TCR+, γδ TCR+ cases are also included in the general category of T-LGL leukemia. At present, it is unclear whether these should continue to be included in this group because recent studies have shown that many types of γδ TCR+ leukemias and lymphomas have distinct, and typically worse, clinical outcomes than αβ TCR+ counterparts (see “Differential Diagnosis”).

Image 4A. Flow cytometric histograms of a case of T-cell large granular lymphocyte (T-LGL) leukemia. In all histograms, a smaller population of normal lymphocytes is also seen. A distinct population of cells showing coexpression of CD5 (a pan-T-cell marker) and CD57 (typically expressed on natural killer [NK] cells) is seen in the upper left histogram. Expression of CD57 on T-cell populations is seen in essentially all cases of T-LGL leukemia. A large population of cells coexpresses CD5 and CD8 (upper right histogram). Only rare cases of T-LGL leukemia express CD4. The large population of T-LGL leukemia cells expresses CD16, which is seen in approximately 80% of cases (lower left histogram). There is no expression of CD56 in this case of T-LGL leukemia, although different degrees of CD5 expression distinguish the neoplastic cells (dim CD5) from the normal T cells (moderate-bright CD5) (lower right histogram). Case contributed by D. Bahler.

Image 4B. Killer cell immunoglobulin-like receptor (KIR) antigen expression profile in large granular lymphocyte (LGL) leukemia. LGL leukemia cells (green) are shown to express CD3 and CD16 in this case, in contrast with normal lymphocytes (red), which do not express CD16 (upper left histogram). The remaining histograms show a uniform lack of expression of CD158a (upper right), CD158b (lower left), and CD158e (lower right). Uniform expression of a single KIR antigen or lack of expression of all KIR antigens is abnormal and is a finding in most LGL leukemias. Case contributed by W. Morice.
Although FC is the preferred method, immunohistochemical staining can be quite useful in demonstrating abnormal T cells in specimens when fresh samples for FC are not available. In tissues with abnormal T-cell infiltrates, immunohistochemical staining for CD3 will highlight the infiltrating cells. Linear and sinusoidal patterns of infiltration may be useful for distinguishing T-LGL leukemia cells from normal reactive T cells. Furthermore, T cells can be evaluated for a variety of T-cell antigens by tissue immunohistochemical staining. T-cell intracellular antigen-1, perforin, and granzyme B, markers of cytotoxic cells including T-LGL, will highlight the abnormal lymphocytes of LGL leukemia. BF1 is an immunohistochemical stain that can be used to demonstrate αβ TCR expression. T-cell lymphoma 1 (TCL1) expression is not seen in T-LGL leukemia. Other specific stains can be used to evaluate for specific differential diagnoses, such as EBV staining in naso-type NK/T cell lymphoma (see “Differential Diagnosis”).

**Molecular Genetics and Cytogenetics**

Clonal abnormalities discovered by routine cytogenetics are quite rare in T-LGL leukemia, with only approximately 20 cases with abnormal cytogenetics reported. Recent studies have reported that inversion of chromosome 14 (associated with the αβ TCR), inv7 (γδ TCR), and deletion of 6q can be seen in LGL leukemias. Other reported abnormalities include +8, +14, and t(11;12). The most common method for establishing clonality in LGL disorders is assessment of TCR gene rearrangements. Polymerase chain reaction (PCR) analysis is most commonly used, although its sensitivity is only 70% to 80% with the most commonly used techniques. When available, Southern blot analysis has increased sensitivity but is more labor-intensive and time-consuming. Oligoclonal expansions of T-LGL can be seen in association with viral infections (EBV and cytomegalovirus) and graft-vs-host disease.

Gene expression arrays have been performed on cases of T-LGL leukemia with overexpression identified in genes encoding proteases: granzyme (A, H, B, K), perforin, cathepsin C, cathepsin W, perforin, caspase 8, and the calpain small subunit. Down-regulated genes included proteolytic inhibitors: cystatin C, cystatin A, α1-antitrypsin, and metalloproteinase inhibitors. Sphingosine-1 phosphate receptor is up-regulated, and it may help prevent leukemic cells from undergoing apoptosis.

**Variant Forms of LGL Leukemia**

There are 3 notable variants of T-LGL, based primarily on immunophenotypic differences. These are rare, and it is unclear whether they have significantly different clinical findings to justify being classified as distinct entities. CD4+ T-LGL leukemia differs from typical T-LGL leukemia in that 80% of patients have normal physical examination findings, with only rare splenomegaly but somewhat frequent lymphadenopathy. These cases lack neutropenia, anemia, and splenomegaly in contrast with most CD8+ T-LGL leukemias. There is no apparent association with rheumatoid arthritis or other rheumatologic diseases. However, association with other malignancies is frequent. Of 33 patients, 6 (18%) had a concomitant B-cell lymphoproliferative disorder, 3 (9%) had nonhematologic malignancies, and 1 had hematologic and nonhematologic malignancies in addition to a CD4+ T-LGL leukemia.

It has been suggested that CD8+ T-LGL leukemias that coexpress CD56 have more aggressive clinical behavior. In a study by Gorczyca et al, 35% of T-LGL cases tested were CD56+, suggesting that this finding is not uncommon. A case report discussed transformation of a CD56+ variant of T-LGL leukemia to an aggressive peripheral T-cell lymphoma with CD30 expression. Although large studies do not exist, cases of T-LGL leukemia that express CD56 may require closer follow-up, with an eye toward aggressive clinical behavior.

As mentioned, cases of γδ T-LGL leukemia (CD8+) exist but are rare in comparison with αβ T-LGL leukemias. The immunophenotype of γδ T-LGL leukemia varies somewhat from that of the typical αβ type: CD3+, CD2+, CD4–, CD8 variable (38%), CD5 variable (60%), CD7 variable (100%), CD16+ in most cases (86%), CD56 variable (38%), and CD57 variable (57%). In comparison with other γδ lymphoproliferative disorders, γδ T-LGL leukemias have an excellent prognosis and are considered an indolent disease. However, studies directly comparing αβ T-LGL leukemia have not been reported.

**Pathobiology**

The cells of T-LGL leukemia show the same features as antigen-activated T cells and seem to retain some of the physiologic properties of their normal counterparts. It is thought that the underlying initiator of T-LGL leukemia may be chronic immune stimulation (as in rheumatoid arthritis). Cells undergo malignant transformation through somatic mutation, with chromosomal abnormalities or possibly human T-lymphotropic virus 1 or other retroviruses as possible initiators. In analysis of T-LGL leukemias, in comparison with other T-cell proliferations, a single dominant and several other weak additional gene products were found when testing for Vp transcripts. This supports the idea that T-LGL leukemias may arise out of polyclonal or oligoclonal proliferations. This may occur as a result of dysregulation of apoptosis through Fas pathways or other mechanisms.

CD8+ T cells function through major histocompatibility complex (MHC)-mediated interactions. This is in contrast with NK cells that, although they share features with cytotoxic T cells, normally function through MHC-independent
mechanisms. Normal effector T cells express Fas ligand (Fas-L), a member of the tumor necrosis family. Fas-L and Fas interactions on target cells initiate apoptosis. T-LGL leukemia cells are resistant to Fas-mediated apoptosis. Also, high levels of circulating Fas and Fas-L are seen in patients with T-LGL leukemia. Soluble Fas may block Fas-mediated apoptosis of tumor cells with T-LGL leukemia cell accumulation as a result of resistance to apoptosis. Correlation exists between disease activity and Fas-L levels, with reduction in Fas-L levels in treated patients.

TCR Vβ and Killer Cell Immunoglobulin-like Receptors

As mentioned, establishing clonality of T-LGL proliferation is an important cornerstone to diagnosis. Three methods that can be used for this purpose are PCR, Southern blot analysis, and FC to evaluate the Vβ TCR repertoire. PCR and Southern blot analysis to assess the clonality of the TCR genes are well discussed elsewhere in many reviews. Herein, the focus is on immunophenotypic approaches to assessing T-cell clonality.

In most normal circumstances, T cells show a distribution of Vβ products representing a polyclonal pattern. In T-LGL leukemia, there is a dominant population that expresses a single Vβ pattern. However, there are reactive conditions in which Vβ expression may become more restricted and oligoclonal or even have a single dominant clone. By using these sensitive techniques, it is possible to find small T-cell “clones” in populations that do not have other clinical features of T-LGL leukemia, including patients with autoimmune disorders, elderly patients, and some patients with viral infections. It is possible that these restricted T-cell populations are normal immune responses to specific stimuli, but in some cases, these may represent preclinical or precursor lesions to T-LGL leukemia. Furthermore, although rare, T-LGL leukemias may have more than one Vβ subtype that is clonal.

Advantages of FC Vβ testing include rapid turnaround time, quantitative and qualitative evaluation of the T-cell repertoire, evaluation of specific populations by combining Vβ testing with other immunophenotypic markers, and a commercially available panel of Vβ markers for FC. Vβ test results by FC are considered clonal if more than 50% of T cells express 1 Vβ subtype and suggestive of clonality if 40% to 49% are of 1 Vβ subtype or if more than 70% of tested cells fail to react with any of the Vβ subtypes tested. Testing using FC methods for Vβ detects approximately 80% of clonal T-cell disorders compared with “gold standard” results by molecular assessment of TCR gene clonality.

No specific Vβ subtype is associated with T-LGL leukemia. In T-LGL leukemias associated with rheumatoid arthritis, Vβ6 expression was not increased. This information supports the hypotheses that some cases of T-LGL leukemia are antigen-driven and that not all cases have the same underlying antigenic trigger.

Another important area of development in evaluation of T-LGL leukemia and related disorders is the evaluation of T and NK cells for killer cell immunoglobulin-like receptors (KIRs). KIRs are involved in recognition of MHC class I molecules and self-tolerance of antigen. KIRs are members of the immunoglobulin superfamily and consist of 12 members encoded by a single gene located at chromosome 19p13.4. KIRs are stably expressed throughout the lifetime of T and NK cells. In most cases of T-LGL leukemia, single, uniform-intensity expression of a KIR antigen is seen. Occasionally, however, expression of several KIRs and, in some cases, partial expression of KIRs by T-LGL cells is seen. Furthermore, KIR antigens expressed on T-LGL leukemias are frequently different from those predicted based on HLA-1 phenotypes. When there is a match between HLA-1 and KIRs, the patients are more frequently asymptomatic.

Differential Diagnosis

The differential diagnosis of T-LGL leukemia is dominated by other T- or NK-cell neoplasms with leukemic manifestations. Diagnoses to consider include T-prolymphocytic leukemia (T-PLL), hepatosplenic T-cell lymphoma, extranodal NK/T-cell lymphoma of the nasal type, aggressive NK-cell leukemia, and chronic NK lymphocytosis.

T-PLL is usually associated with a relatively rapid onset and an aggressive clinical course. Rare cases of T-PLL may be CD8+ (15%), but most cases are CD4+ or CD4+/CD8+. Cytogenetic abnormalities are seen in most cases, and TCL1 staining is positive, in contrast with T-LGL leukemia. Hepatosplenic T-cell lymphoma may have similar sites of involvement (PB, BM, and spleen) but is more frequent in younger patients and has a more aggressive clinical course. Also, it differs from T-LGL leukemia in immunophenotype (most cases are CD4-/CD8–) and the presence of isochromosome 7q.

There is considerable overlap in the immunophenotype of T-LGL leukemia and extranodal nasal-type NK/T lymphoma. Furthermore, a leukemic form of the latter entity exists. Significantly different findings in extranodal nasal-type NK/T lymphoma include the frequent presence of CD56, lack of CD8 expression, and EBV positivity. It is thought that the entity aggressive NK-cell leukemia may correspond to a leukemic form of extranodal NK/T lymphoma of the nasal type and would have comparable differences with T-LGL leukemia.

Chronic NK-cell lymphocytosis contrasts with other NK leukemias in its rarity, indolent course, and, in some cases, complete lack of symptoms. It may even spontaneously resolve. The indolent clinical behavior and natural history
are similar to those of CD8+ T-LGL leukemias.55 Cytopenias are less frequent than in CD8+ T-LGL leukemias. On average, approximately 60% of circulating lymphocytes are NK cells, with a mean value of $4.8 \times 10^9/L$.55 Of 6 cases in 1 study, 4 appeared to be clonal by KIR analysis, and this would suggest an indolent NK leukemia.55

Summary

T-LGL leukemias are a well-described group of indolent neoplasms thought to derive from chronic antigen stimulation in some cases. There is a strong association with autoimmune diseases. Clinically, patients have lymphocytosis, cytopenias of other lineages, and increased frequency of infections. The PB, BM, and spleen are frequently involved and have characteristic morphologic findings. Diagnosis is typically based on finding an abnormal immunophenotype by FC. New techniques, such as $V_\beta$ testing and KIR expression, may enhance diagnosis and our understanding of T-LGL leukemia and related disorders.

References


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