HHS Public Access

Author manuscript

Hematol Oncol. Author manuscript; available in PMC 2015 March 29.

Published in final edited form as:

Hematol Oncol. 2010 September ; 28(3): 105–117. doi:10.1002/hon.917.

The root of many evils: indolent large granular lymphocyte leukemia and associated disorders

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Abstract

Large granular lymphocyte (LGL) leukemia can arise from either natural killer (NK) cells or cytotoxic T lymphocytes (CTL). The T-cell form of LGL leukemia has significant overlap with other hematological disorders and autoimmune diseases. Here we provide an overview of LGL biology. We also focus discussion on the indolent LGL leukemia related disorders and their causal relationships. We then discuss the potential relationships and distinctions between indolent LGL leukemia and non-malignant clonal lymphocyte expansion that occur in otherwise healthy individuals, especially elder people.

Keywords

large granular lymphocyte leukemia; autoimmunity; non-malignant clonal lymphocyte expansion

Large granular lymphocyte biology 101

The term “large granular lymphocytes” (LGL) refers to a morphologically distinct subpopulation that normally comprises 10%–15% of peripheral blood mononuclear cells (PBMC). LGL are characterized by high cytoplasmic:nuclear ratio and abundant azurophilic granules. [1, 2] Despite initial characterization of LGL as natural killer (NK) cells, LGL are now shown to contain both cytotoxic T lymphocytes (CTL, CD3+) and NK cells (CD3−), both of which belong to the lymphoid lineage and serve as the main executors of cell-mediated cytotoxicity. [3–5]

The antigen-specificity of LGL varies with cell types. NK cells, which belong to the innate immune system, possess the least antigen specificity. They are “naturally” armed with cytolytic granules and chronically exhibit the LGL morphology. Their activation does not require interaction with a specific major histocompatibility complex (MHC) – peptide complex. Rather, it depends on the relative signaling strength downstream of the activating and inhibitory NK receptors. The activity of inhibitory NK receptors maintains the resting state of NK cells. Upon encountering non-healthy-self targets such as tumor cells or virus infected cells, activating NK receptors are triggered. NK cells are eventually activated once

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

the balance between activating and inhibitory signaling is broken. [6, 7] Due to their surface expression of the low affinity Fc receptor (CD16), NK cells can also participate in antibody-dependent cell cytotoxicity. [8] Traditionally, NK cells were considered to function primarily at the front line of defense because of their almost immediate target-lysis activity and limited proliferation capability after activation. [4] However, it has been reported that the $CD56^{bright}$ NK population exhibited limited cytotoxicity yet enhanced cytokine secretion and proliferation ability, pointing to their regulatory function. [9] CTL, on the other hand, have relatively stringent antigen-specificity, with αβ lineage more stringent than γδ lineage. αβ T cells and γδ T cells were suggested to share common CD4−CD8− double negative precursors. It is believed that the lineage differences arise after T-cell receptor (TCR) recombination during T-cell development. Cells productively rearrange TCR- γδ differentiate into γδ T-cells and cells successfully rearrange TCR-β mature into αβ T-cells, although the exact mechanisms remain unknown. [10] With increased TCR variety, the activation of αβ-CTL strictly depends on their recognition of specific MHC-peptide complex. They function primarily in the adaptive immune system. On the contrary, γδ-CTL have limited TCR variety yet possess the ability to respond to intact antigen. This feature places them at the intersection between innate and adaptive immune responses. [11] Different from the immediate cytolytic activity of NK cells, both αβ- and γδ-CTL require an activation phase to acquire cytotoxicity and LGL morphology. However, both CTL lineages can undergo extensive expansion after activation, granting them a major role in response to prolonged antigen stimuli or high antigen loads. [4]

Upon activation, there are two major pathways through which LGL execute their targets: granule-mediated pathway and receptor-mediated pathway. [4, 12] Granule-mediated pathway depends on the exocytosis of the cytolytic granules of LGL to induce lysis and apoptosis of the target cells. Upon target recognition, granules are polarized towards the immune synapse where LGL interact with targets. Two major components of cytolytic granules are the pore-forming protein perforin, and a family of serine proteases – granzymes. [13] Perforin, in addition to directly inducing osmotic lysis by forming pores on the target cell membrane, is indispensable for granzyme delivery and activity within target cells. [12, 14] Granzymes, with their protease activity, potentiate the death fate of target cells by cleaving and activating the effector caspases as well as pro-apoptotic Bcl-2 family members. [15] The receptor-mediated pathway relies on the engagement and activation of death receptors, such as Fas (APO-1, CD95), by their ligands. Death receptors are universally expressed on various cell types, while the corresponding ligands are usually elevated on activated LGL. [16] This pathway is not specific for the immune system, and the death receptor-ligand interaction is not MHC-restricted. Instead, LGL-target interaction brings target cells to the proximity of LGL. In addition, it has been reported that LGL can manipulate death receptor expression on the targets which optimizes execution. [17] Upon ligation, death receptors cluster and induce the formation of death inducing signaling complex (DISC), which initiates similar signaling cascade as granzymes. [16, 18] Granule-mediated pathway can be instantly activated upon target recognition, although replenishing the granules takes time. [4, 19] On the other hand, death ligands have extended functional half-life, although a time lag is usually required for their optimum expression on LGL after activation. [4, 20, 21] Together, granule-mediated pathway provides an instant and potent

cytolytic force, while the receptor-mediated pathway serves as a gentle yet persistent complement.

Both granule-mediated pathway and receptor-mediated pathway contribute to the LGL elimination after activation, which is termed activation-induced cell death (AICD). Granule-mediated pathway can act on the activated LGL through endocellular or extracellular granule leakage, which triggers similar signaling pathways as in the target cells. [22, 23] Receptor-mediated pathway follows the same strategy. After activation, LGL express elevated death receptors, making themselves sensitive to the death ligands. [16, 24] AICD can occur in a suicide fashion and among LGL from the same or different lineage. [16, 25] To ensure sufficient LGL activity prior to AICD, a delicate resistance system exists. [16, 22, 26] It enables the titration of AICD process and allows the elimination of LGL to occur only after antigen clearance.

Large granular lymphocyte leukemia

LGL leukemia, as implied by the name, refers to the abnormal expansion of LGL in peripheral blood often accompanied by infiltration of marrow, spleen and liver. [27] Based on cell origins, LGL leukemia can be divided into NK-cell LGL leukemia (NK-LGL leukemia) and T-cell LGL leukemia (T-LGL leukemia), with the latter further divided into αβ- (mainly CD4−CD8+) or γδ- (mainly CD4−CD8− or CD4−CD8+) T-LGL leukemia. A more comprehensive review of this disease was provided elsewhere. [27] The molecular signatures of leukemic LGL resemble chronically activated LGL, competent in cytotoxicity. Yet, they are deficient in proliferation and are resistant to receptor-mediated AICD. [28–33] Both T and NK forms of LGL leukemia exhibit skewed expression of NK activation receptors [34, 35]. Elevated chemokines, cytokines and death receptor ligand (Fas ligand, FasL) are also observed in patient sera [32, 36]. Other serologic abnormalities, including high titers of rheumatoid factor, anti-nuclear antibody, antineutrophil antibody, antiplatelet antibody and circulating immune complexes are frequently detected in LGL leukemia patients. [37]

Clonal expansion is usually a hallmark for neoplasm. However, in the case of lymphocytes, clonal expansion can be a normal process after encountering antigen. Thus, more caution needs to be taken to distinguish transient immune response and persistent malignancy. The clonality of LGL leukemia is readily confirmed by a specific TCR rearrangement pattern in T-LGL leukemia; or a specific Epstein-Barr virus (EBV) genomic integration site in acute NK-LGL leukemia. [38–40] However, other than rare aggressive cases [41, 42], most LGL leukemia patients bear an indolent clinical course, with approximately one third of them asymptomatic at the time of diagnosis. [43] Most patients seek medical care because of LGL leukemia associated conditions (as discussed below), and can be successfully treated by immunosuppressive therapies. [27, 44] Transformation from indolent to aggressive LGL leukemia is very rare [45, 46]. In light of the non-malignant lymphocyte clonal expansion in elder people, the malignant nature of indolent LGL leukemia, particularly αβ-T-LGL leukemia has been questioned. [47, 48] Here, we summarize the clinical features of indolent LGL leukemia by reviewing its associated medical conditions (Table 1) and their causal relationships.

Disorders related to indolent LGL leukemia

Hematological disorders

Indolent LGL leukemia is frequently associated with other hematological disorders, including disorders arising from both lymphoid and non-lymphoid lineages. Lymphoid disorders are primarily associated with indolent T-LGL leukemia and occur in the form of B-cell dyscrasias. [49] The most common B-cell dyscrasia is monoclonal gammopathy of unknown significance (MGUS), in association with both αβ- and γδ-T-LGL leukemia (3%–19%). [49–52] B-chronic lymphocytic leukemia (B-CLL) also occurs together with αβ- and γδ-T-LGL leukemia, but to a less extent (2%–5%). [49, 50] Other associated B-cell dyscrasias reported include follicular lymphoma [49], hairy cell leukemia [49, 51, 53], mantle cell lymphoma [54], small B-cell lymphocytic infiltrate [51], lymphoplasmacytic lymphoma [49, 51], plasmablastic myeloma [51], B-cell acute lymphoblastic leukemia [50] and Hodgkin disease [54]. In addition, hypergammaglobulinemia without other B-cell abnormalities and hypogammaglobulinemia are frequently observed in LGL leukemia patients [49]. In rare cases, it has been reported that more than one form of LGL leukemia occur, such as concomitant αβ- with γδ-T-LGL leukemia [50], and T-LGL leukemia with NK-LGL leukemia [55]. The coexistence of these lymphoid disorders and indolent LGL leukemia are of particular interest because it supports the hypothesis that LGL leukemia results from chronic immune response. Along this lwine, one explanation is that the expansion of immune compartments from several lineages may be caused by normal immune responses against a neoplastic expansion from one lineage. A parallel explanation is that a chronic immune insult such as virus infection causes abnormalities in multiple lineages. [49] Neither explanation suggests a causal relationship between LGL leukemia and other lymphoid disorders. However, identifying the common trigger(s) of the chronic immune response may shed light on the pathogenesis of both.

Another major branch of LGL leukemia associated hematological abnormalities involves various cytopenias and bone marrow failure syndromes. In this category, the most common association in the western world is acquired neutropenia, which affects 70–80% of T-LGL leukemia patients [27, 56, 57], and to a lesser extent NK-LGL patients [58]. In fact, neutropenia related infection is one major reason why LGL leukemia patients seek medical attention. [27] Because of its prevalence, co-occurrence of LGL leukemia and neutropenia is intensively studied.

Acquired neutropenia can be induced by proliferation deficiency (insufficient neutrophil production) or survival deficiency (increased neutrophils destruction). The latter is further divided into splenic sequestration/destruction and peripheral destruction. Despite the frequent presence of splenomegaly [37], splenic sequestration/destruction is unlikely to cause the LGL leukemia associated neutropenia. This is because: 1) the lack of histological evidence for the accumulation or destruction of neutrophils in patient spleen; 2) no correlation shown between the degree of splenomegaly and neutropenia. [59]

Both proliferation deficiency and peripheral destruction are considered plausible reasons for the association of LGL leukemia and neutropenia. Myeloid hypoplasia is frequently observed in LGL leukemia patients, and is potentially cause by the bone marrow infiltration

of leukemic LGL. Marrow involvement by leukemic LGL occurs in an interstitial pattern and is best appreciated by immunohistochemical staining. Linear assays of intravascular CD8+, TIA-1+, grazyme B lymphocytes appear specific for LGL leukemia. [60] However, the relationship between the degree of LGL bone marrow infiltration and the severity of neutropenia has not been well studied. [37, 59] Antineutrophil antibodies are usually detected in LGL leukemia patient sera, suggesting antibody-mediated neutrophil destruction. [43] Monoclonal or oligoclonal CTL expansion and increased CTL cytotoxicity was detected in patients with acquired neutropenia even without frank LGL leukemia. [61] This indicates the presence of MHC-restricted neutrophil destruction, and raises the possibility of a similar pathogenesis occurring in the broader group of patients diagnosed with idiopathic neutropenia. Meanwhile, sera from T-LGL patients, which contain high level of soluble FasL, effectively induced apoptosis of normal neutrophils through the receptor-mediated target execution pathway, and blocking this pathway reduced neutrophil apoptosis. [62] This infers MHC-unrestricted neutrophil destruction in LGL leukemia.

As a further evidence of the causal relationship between LGL leukemia and neutropenia, immunosuppression is usually effective in alleviating neutropenia in LGL leukemia patients. The efficacy of this treatment was shown to correlate with the reduction of clonal LGL and serum level of FasL. [27, 62] On the contrary, stimulation of granulocyte production alone using granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) does not result in sustained clinical improvement of neutropenia in all LGL leukemia patients. [59] The clonal expansion, bone marrow infiltration and abnormal immune activity of leukemic LGL is indispensable for the onset of neutropenia in LGL patients. In fact, LGL leukemia is considered one of the major causes of acquired neutropenia. [63]

Interestingly, neutropenia is a relatively less common association with T-LGL leukemia in the eastern world. Instead, pure red cell aplasia (PRCA), which is common but less prevalent than neotropenia in the western world [56, 64–66], is prominently associated with T-LGL leukemia. [67–70] It is increasingly clear that chronic cytotoxicity of leukemic T-LGL and its bone marrow infiltration are the causes of PRCA, although the surface abnormality of erythroid progenitors may also contribute to this association. Erythroid progenitor colonies from PRCA patients were shown to be more susceptible to leukemic LGL-mediated cytotoxicity due to their low expression of HLA class I molecule, a ligand of killer-cell inhibitory receptors expressed on LGL. This cytotoxicity was shown *in vitro* as an MHC-unrestricted target lysis [71]. Not surprisingly, controlling the leukemic T-LGL clone through immunosuppression benefits or brings complete remission in PRCA patients. [69, 72, 73] It has been suggested that parvovirus B19 plays a role in pathogenesis in PRCA. [74, 75] Interestingly, serum reactivity against B19 and B19 DNA has been detected in some LGL leukemia patients with PRCA. [76, 77] The different clinical phenotype of LGL leukemia in western and eastern world is quite remarkable. This finding suggests that different genetic backgrounds, immune or environmental insults, or both, may render different populations susceptible to different disease manifestations of LGL leukemia.

In addition to neutropenia and PRCA, both T- and NK-LGL leukemia can be associated with other hematologic problems such as hemolytic anemia (HA) [49, 50, 52, 58, 78], aplastic

anemia (AA) [66, 79, 80], paroxysmal nocturnal hemoglobinuria (PNH) [49, 79, 81]; thrombocytopenia including amegakaryocytic thrombocytopenia [58, 78, 82–84]; as well as myelodysplastic syndromes (MDS) [49, 52, 84–87]. There is clinical overlap in these bone marrow failure syndromes. Interestingly, co-occurrence of these disorders can be observed in the same LGL leukemia patient [78], and in rare cases increase of some lineages and decrease of other lineages [88]. A possible explanation of these observations is that the suppression effect exerted by leukemic LGL is on a hematopoietic stem cell (HSC) or a progenitor. Indeed, it has been proposed that abnormalities of marrow progenitors, as occurring in MDS, trigger the initial infiltration and clonal expansion of LGL, and the following pathological immune attack launched by leukemic LGL results in proliferation deficiency as seen in neutropenia, thrombocytopenia, AA and PRCA. [87] Constant survival pressure on hematopoietic progenitors or HSC can also lead to out-growth of abnormal myeloid clones with increased resistance to LGL-mediated suppression but abnormal hematological functions, as seen in PNH. [87] Same scenario appears to be applicable in the case of NK-LGL leukemia associated with neutropenia and thrombocytopenia in the context of bone marrow granuloma. [89]

In addition to LGL bone marrow infiltration, decreased blood cell survival from splenic sequestration may also play a role in LGL leukemia associated cytopenias, particularly anemia and thrombocytopenia. This is potentially due to the differences of life span and destruction sites among erythrocytes, platelets and neutrophils. Circulating neutrophils have an average half life of 7 hours, and the damaged neutrophils are normally cleared during peripheral circulation and in the lung. [90] In contrast, mature erythrocytes and platelets have an average life span of 120 days [91] and 7 days respectively, while spleen is one of the primary sites of “quality control” and destruction [91, 92]. Increased “screening” time that erythrocytes and platelets spend in the spleen makes anemia and thrombocytopenia potential consequences of splenomegaly. Patients with LGL leukemia often have splenomegaly, which could potentiate anemia and thrombocytopenia, either by promoting splenic sequestration or direct destruction. [59] As in the case of neutropenia, the detection of antiplatelet antibody and circulating immune complexes in LGL leukemia patient sera suggested the involvement of peripheral destruction. [37] Not surprisingly, splenectomy has resulted in sustained clinical benefit for some LGL leukemia patients with autoimmune HA [93] and thrombocytopenia [94].

The association of LGL leukemia with acquired periodic hematological disorders, including cyclic neutropenia (CN) [95–97] and cyclic thrombocytopenia (CT) [98, 99] is extremely rare. However, it provides a niche to dissect the casual relationship between LGL leukemia and most of its associated non-lymphoid hematological disorders. In general, hematopoiesis is regulated by growth factors that reflect the peripheral requirement. Thus, there is a lag between the presence of needs and the initiation of HSC/progenitor proliferation. As other negative control systems with a delay, hematopoiesis has a tendency to oscillate. [100] The transition from hematological homeostasis (a stable state) into periodic hematological disorders (a periodically oscillating state) and the effect of proliferation or survival deficiency on this transition can be mathematically analyzed. Model simulations revealed that as blood cells spend more time in periphery than bone marrow, in the sequence of neutrophils, platelets and erythrocytes, the influence of a survival defect to the

corresponding periodic disorders increases, while the importance of a proliferation defect decreases. [100, 101] Interestingly, it was reported that immunosuppression normalized neutrophil count in LGL leukemia associated CN. Yet, similar treatments had limited effect on platelet count and the cycling time in LGL leukemia associated CT. [95, 98, 99] Taken together, these data support the notion that LGL leukemia contributes to its associated hematological disorders primarily through inducing a proliferation defect.

Other hematological conditions associated with LGL leukemia patients have also been reported, including hereditary hemochromatosis [102, 103], splenic marginal zone lymphoma [50], peripheral T lymphoma [104], familial (congenital) pancytopenia with interstitial pneumonia [105] and Wiskott-Aldrich syndrome (WAS) [106–108]. Among these, the association between WAS and LGL leukemia represents another possible pathogenic mechanism. WAS is a rare X-linked immunodeficiency disorder caused by *WASP* gene mutation. *WASP* is an important regulator of actin polymerization. As seen in WAS patients, *WASP* mutation induces thrombocytopenia with small platelets, eczema, increased incidence of autoimmune manifestations and malignancies. In rare cases, spontaneous reversion of this mutation or second gain-of-function mutation can occur in WAS patients. [108, 109] If occurring in LGL, this somatic mosaicism can grant clonal LGL growth advantage [106, 108] and may eventually lead to the leukemia state [107].

Autoimmune disorders

LGL leukemia is known to be associated with a wide spectrum of autoimmune disorders, with most of them involving connective tissue. Roughly, these disorders can be divided into arthropathies, vessel and skin disorders, neuropathies, muscular and glandular disorders, and other connective tissue disorders. Arthropathies associated with LGL leukemia primarily contain rheumatoid arthritis (RA), the most common autoimmune disease associated with T-LGL leukemia in the western world. [37, 49, 50, 52, 110–114] RA is reported in about one third of T-LGL leukemia patients [27], compared to its presence in 0.5%–1% adult population worldwide [115]. Interestingly, this association is rarely reported in NK-LGL leukemia patients [58, 116], although arthralgia can occur [58]. It is also worth noting that RA has a less frequent association with LGL leukemia in eastern world. [67] This phenomenon cannot be explained by the differences of RA incidences in different populations. [115]

Felty's syndrome, a specific sub-category of RA featuring the co-occurrence of RA, neutropenia and splenomegaly, is frequently associated with T-LGL leukemia. [59, 117] In fact, LGL leukemia patients with neutropenia and RA closely resemble patients exhibiting Felty's syndrome and T-cell clonal expansion [59]. Due to the prevalence of the immunogenic marker HLA-DR4 in both diseases, it has been suggested that Felty's syndrome and LGL leukemia with RA are part of a single disease process. [111] However, the causal relationship between RA and T-LGL leukemia is less clear. Lymphocyte infiltration at the synovial lesions in RA is potentially antigen driven, and subsequent ectopic lymphoid follicle formation is frequently observed. However, the dominant population of lymphocytes is CD4+ T cells. [115, 118] A small group of synovial-specific CD40 ligand (+) perforin (−) CD8+ T cells have been implicated in RA pathogenesis.

Although they are essential in maintaining the germinal center of ectopic lymphoid follicle as well as the immune activity of CD4+ T cells and B cells [118], their phenotype and distribution is different from that of leukemic T-LGL [28]. On the other hand, RA is associated with distorted cytokine network, with elevated expression of cytokines promoting the activation and survival of cytotoxic lymphocytes, including interleukin (IL) – 15. [115, 119, 120] Similar cytokine profile is also observed in T-LGL leukemia patients. [36] Recently, network modeling of the survival signaling in T-LGL leukemia revealed that IL-15 is indispensable for the long-term survival of leukemic T-LGL. [121] One hypothesis to explain a link between LGL leukemia and RA would be exposure to a common inciting antigen. Alternatively, this association may be due to the distorted cytokine network in RA which maintains the long-term survival of leukemic LGL.

The usual association of T-LGL leukemia and RA rather than with NK-LGL leukemia might be explained by the initial antigen-specific and MHC-restricted activation of CTL rather than NK cells. In RA, NK cells in synovial fluid have reduced expression of perforin, KIR and functional activity [122, 123].

Vessel and skin disorders can occur in association with T- and NK-LGL leukemia and include pulmonary artery hypertension (PAH) [35, 124, 125], generalized pruritus [126], vasculitis [58, 104, 127], aphthous ulcer [58, 104], livedo reticularis (livedoid vasculopathy) [58, 104], pityriasis lichenoides [128], scleroderma (systemic sclerosis) [129], vascular mammary skin lesion [130], psoriasis [50], and allergic skin involvement [58, 83, 130]. Cutaneous findings occur more frequently in NK-LGL leukemia patients than T-LGL leukemia patients [104]. LGL infiltration is often observed in diseased areas [35, 58, 125]. Moreover, different from NK cells or CD8+ T cells isolated from healthy donors, leukemic LGL isolated from T- or NK-LGL patients with PAH are competent to lyse endothelial cell lines derived from normal pulmonary artery [35, 125]. Immunosuppression benefits some patients in this category [124, 125, 130], suggesting infiltration of leukemic LGL to the diseased areas as a potential mechanism for the onset of vessel and skin disorders in LGL leukemia patients.

Neuropathies can present together with LGL leukemia in forms of multiple sclerosis (MS) [94, 131], paraneoplastic neuropathy, and peripheral neuropathy [58, 67, 83, 132, 133]. In several cases, infiltration of leukemic LGL in affected tissues was observed, and treatments such as steroid, FND (fludarabine, mitoxantrone and dexamethasone), and bone marrow transplantation were shown to be effective. [131–133] In terms of the pathogenesis, it has been suggested that neuropathies such as MS may be triggered by an initial infection and distorted immune response. [134] Moreover, certain forms of neuropathies such as HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) can be induced by retroviral infection. [135] Thus, it is possible that LGL leukemia and its associated neuropathies share a common initial immune trigger, and prolonged immune response eventually allows for the escape and expansion of autoreactive LGL, which leads to disease onset.

LGL leukemia associated muscular and glandular diseases occur in forms of myositis [136] and other musculoskeletal symptoms [58], Sjögren syndrome [52, 126, 129, 137, 138], autoimmune thyroiditis (Hashimoto’s disease) [50, 52, 94, 129, 138], autoimmune

polyglandular syndrome (APS) [138], endocrinopathy, Grave's disease (hyperparathyroidism) and Cushing's syndrome. [52, 94] Other connective tissue disorders associated with LGL leukemia involve systemic lupus erythematosus (SLE) [94, 129, 139], Behçet disease [140], uveitis and celiac disease [141]. In these associations, as in RA, T-LGL leukemia is more commonly associated than NK-LGL leukemia.

Viral or non-viral triggers are suggested in most of LGL leukemia associated muscular and glandular diseases. These immune insults potentially induce the characteristic lymphocyte infiltration and adaptive immune system-mediated destruction at the affected tissue in these diseases. [136, 142–144] Even in the absence of lymphocytosis, clonal expansion of CD8+ but not CD4+ T cells and reverted CD8:CD4 ratio was observed at the affected tissues or in the periphery of patients with autoimmune thyroiditis and SLE, suggesting chronic CTL response. Interestingly, decreased circulating NK cells were noted in SLE. [145, 146] Alternatively, chronic lymphocyte activation in these diseases might be caused by genetic mutation, as in the case of APS type I. The mutation of an autoimmune suppressor gene AIRE (for autoimmune regulator) hampers the negative selection process during T cell development, breaking self-tolerance and inducing autoimmunity. [143, 147] Together, it is plausible that the clonal expansion of leukemic LGL in patients of this category is a manifestation of an on-going autoimmune response. [137] It is worth noting that there is significant overlap within this group of diseases. They also overlap with many other hematological, neurological or autoimmune disorders associated with LGL leukemia. [137, 142, 148, 149] These data suggest an underlying role of LGL in various autoimmune diseases..

Other associations

The coexistence of LGL leukemia and other malignancies (including thyroid, lung, liver, colon-rectal, prostate, testicular, melanoma, basal cell carcinoma) [50, 52, 94, 150, 151] as well as non-hematological genetic disorders such as Turner syndrome [152] has been reported. LGL leukemia post transplantation has also been discussed. [153, 154] It is conceivable that the association of LGL leukemia and other malignancies results from shared genetic alterations and failure of immune surveillance. A similar scenario may occur in the association of LGL leukemia and transplantation. The massive immunosuppression post transplantation can hamper immune surveillance and promote the outgrowth of an abnormal leukemic LGL clone. On the other hand, chronic antigen stimulation (tumor antigens, graft antigens or abnormal protein products) is present in most of these conditions. Together, these data suggest that specific genetic alteration or chronic exposure to specific antigen(s) may be needed to initiate the expansion of leukemic LGL. Subsequent transformation of these activated LGL might be required for onset of LGL leukemia.

Non-malignant clonal lymphocyte expansion versus LGL leukemia

Characteristics of non-malignant LGL expansion

Non-malignant clonal lymphocyte expansion primarily refers to the clonal CD8+ αβ-T cell expansion. By definition, it occurs in the absence of absolute lymphocytosis and associated disease. It is a surprisingly common phenomenon in elder people. In some studies, it has

been reported that the expansion of CD8+ T cells with restricted clonality was observed in one third of total population over the age of 65 years. [155] Increased clonal restriction of CD8+ T cells also correlates to reduced portion of the naïve CD8+ T cells and the reversed CD4+:CD8+ ratio observed in elder people. [156] In the case of γδ-T cells, it was reported that an increased cell portion has undergone previous activation [157], which potentially restricts the diversity of antigen recognition. The total number of γδ-T cells is significantly lower in elder people compared to young people, which was due to the decrease of Vδ2 cells. [158] The number of Vδ1 cells is not changed with aging [158], rendering its relative expansion within the γδ-T cell population. On the other hand, with increase in age, there is an increased number of $CD56^{dim}$ NK cells (high NK activity) [159] and a decreased number of $CD56^{bright}$ NK cells [160]. However, the total NK cell number is relatively stable at different ages. [160]

The onset of non-malignant CD8+ T cell clonal expansion in healthy elderly people is potentially due to the combination of immune senescence and molecular alterations in CD8+ T cells. In order to mount successful immune response, clonal expansion is an indispensable process after T cell activation. Despite the existence of AICD process that maintain T cell homeostasis after activation, prolonged immune insult may lead to immune senescence, which hampers T cell proliferation after activation as well as AICD and alters the CD4+:CD8+ ratio. Moreover, it has been shown that the clonally expanded T cells in elderly people have shortened telomere, impaired proliferation ability and resistant to receptor-mediated AICD process. [156, 161] Thus, the persistence of non-malignant T cell clonal expansion is suspected to be the remnant of chronic infection throughout a life time. Cytomegalovirus (CMV) and EBV appear to be enticing candidates for this hypothesis due to their prevalence. T cell clonal expansion was also reported in human immunodeficiency virus (HIV) infected patients. [156] However, there is no known common antigen specificity observed across individuals exhibiting non-malignant T cell clonal expansion. [47]

CD8+ T cell molecular alteration was also proposed to explain the non-malignant T cell clonal expansion in elderly people. As human beings age, certain molecular alterations might occur in CD8+ cells due to intrinsic (genetic alteration) or extrinsic (virus infection) factors, which grants the affected clone growth and survival advantages over its normal counterparts. The altered clone may also undergo further differentiation and form the expanded clonal terminally differentiated T cells (T_{EMRA}) as observed in the peripheral blood of elderly people. The persistence of clonally expanded CD8+ T cells can be antigen dependent or independent. [47] However, a difficulty for this hypothesis is how to explain the preferential CD8+ T cell clonal expansion over other immune compartments. Taken together, it is more likely that both immune senescence and molecular alterations of CD8+ T cells are needed for the persistence of non-malignant CD8+ T cell clonal expansion, while the degree of their contributions might vary in different cases.

Similarities and differences between non-malignant T cell clonal expansion and indolent LGL leukemia

There are significant overlaps between non-malignant T cell clonal expansion and indolent LGL leukemia, particularly CD8+ αβ-T-LGL leukemia. In both cases, the expanded CD8+

T cells are clonal and competent in cytotoxicity. Phenotypically, the dominant CD8+ clones resemble T_{EMRA} and experience telomere shortening. They showed impaired proliferation as well as AICD after *in vitro* stimulation [28, 30, 156, 162]. Both expansions are suggested to be triggered by an initial immune response. The expanded clones present chronically rather than transiently, and occur primarily in elderly people.

With this said, there are distinct features of CD8+ αβ-T-LGL leukemia as well as LGL leukemia in general compared to non-malignant T cell clonal expansion. First, bone marrow and tissue infiltration of leukemic LGL, which can be interpreted as a form of invasion, is absent in non-malignant T cell clonal expansion by definition, although the destruction cause by this “invasion” in LGL leukemia is not through “replacement” but through immune response [59]. Second, lymphocytosis, which is common in LGL leukemia patients, is by definition absent from non-malignant T cell clonal expansion. This suggests the loss of homeostasis in LGL leukemia but not non-malignant T cell clonal expansion. Third, the wide-spread hematological disorders and autoimmune diseases associated with LGL leukemia suggest the acquisition of autoreactivity of leukemic LGL, while non-malignant T cell clonal expansion by definition does not lead to autoimmunity. Finally, unlike clonal expansion of CD8+ αβ-T cells observed in aging population, a similar expansion of γδ-T cells or NK cells is not seen. Thus, it is more likely that LGL leukemia exists as a unique clinical entity which is different from the non-malignant T cell clonal expansion observed in elderly people, although they might share common initiation mechanisms.

Conclusion

LGL leukemia is characterized by abnormal clonal expansion of mature LGL that remain long-term competent. In this review, we provide an overview of conditions associated with this rare leukemia, particularly the indolent form. We also discuss underlying mechanisms for these associations. This review outlines clinical presentations where the presence of LGL leukemia can be suspected.

Going back to the initial discussion of the malignancy of indolent LGL leukemia, despite an absence of consistent genetic disorders [27], a survival advantage of the clonal leukemic LGL over their normal counterparts is clearly seen in patients. Moreover, tissue invasion is a common feature of leukemic LGL, which leads to the wide spectrum of LGL leukemia associated hematological and autoimmune disorders. Together, as suggested previously [28], although the exact survival mechanisms of leukemic LGL are unknown, the evidence presented in this review points indolent LGL leukemia to the intersection of malignancy and autoimmunity, suggesting the possibility of a common pathogenesis in LGL leukemia and many hematological disorders as well as autoimmune diseases.

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Table 1

Summary of conditions associated with indolent LGL leukemia

Name of the medical condition		Associated subtype (s) of LGL leukemia	Reference	Comment
B-cell conditions	Monoclonal gammopathy of unknown significance (MGUS)	αβ-T; γδ-T	[49–52]	
	B-chronic lymphocytic leukemia (B-CLL)	αβ-T; γδ-T	[49, 50, 163]	[163] is a case of CD56+ variant of T-LGL leukemia
	follicular lymphoma	αβ-T	[49]	
	hairy cell leukemia (HCL)	αβ-T	[49, 51, 53]	
	mantle cell lymphoma (MCL)	T	[54]	Clonality unknown
	small B-cell lymphocytic lymphoma	αβ-T; γδ-T	[51]	
	lymphoplasmacytic lymphoma	αβ-T	[49, 51]	
	plasmablastic myeloma	γδ-T	[51]	
	B-cell acute lymphoblastic leukemia (B-ALL)	γδ-T	[50]	
	Hodgkin disease	T	[54]	Clonality unknown
	polyclonal-hypergammaglobulinemia	αβ-T	[49]	
	hypogammaglobulinemia	αβ-T	[49]	
LGL leukemia	αβ-T-LGL leukemia	γδ-T	[50]	
	αβ-T-LGL leukemia	NK	[55]	
cytopenia and anemia	neutropenia	αβ-T; γδ-T; NK	[27, 56–58]	
	anemia including hemolytic anemia (HA)	αβ-T; γδ-T; NK	[49, 50, 52, 58, 78]	
	thrombocytopenia including amegakaryocytic thrombocytopenia and immune thrombocytopenic purpura (ITP)	αβ-T; γδ-T; NK	[58, 78, 82–84]	
bone marrow failure syndrome	pure red cell aplasia (PRCA)	αβ-T; γδ-T;	[50, 56, 64–70, 110, 113, 114]	
	aplastic anemia (AA)	αβ-T;	[79, 80]	
	paroxysmal nocturnal hemoglobinuria (PNH)	αβ-T;	[49, 79, 81]	
	myelodysplastic syndromes (MDS)	αβ-T; NK	[49, 52, 84–87]	
periodic hematological disorders	cyclic neutropenia (CN)	αβ-T	[95–97]	
	cyclic thrombocytopenia (CT)	T	[98, 99]	
other hematological disorders	hereditary hemochromatosis	αβ-T	[102, 103]	[102] is a case of CD3+CD56+CD57- αβ-T-LGL leukemia
	splenic marginal zone lymphoma	γδ-T	[50]	
	peripheral T cell lymphoma	NK	[104]	
	congenital pancytopenia with interstitial pneumonia	NK	[105]	
	Wiskott-Aldrich syndrome (WAS)	γδ-T; NK	[106–108]	lymphocyte expansion in [108] affects both T an NK sub-population

Name of the medical condition		Associated subtype (s) of LGL leukemia	Reference	Comment
autoimmune disorders (arthropathies)	rheumatoid arthritis (RA) and Felty's syndrome	αβ-T; γδ-T; NK	[37, 49, 50, 52, 58, 110–114, 116]	NK-LGL leukemia is rarely associate with RA
autoimmune disorders (vessel and skin)	pulmonary artery hypertension (PAH)	αβ-T; NK	[35, 124, 125]	
	generalized pruritus	T	[126]	32% lymphocytes are CD56+CD57+
	vasculitis	αβ-T; NK	[58, 104, 127]	[127] is a case of CD3+CD4+CD8+CD56+ αβ-T-LGL leukemia
	aphthous ulcer	NK	[58, 104]	
	livedo reticularis (livedoid vasculopathy)	NK	[58, 104]	
	pityriasis lichenoides	T	[128]	
	scleroderma (systemic sclerosis)	αβ-T	[129]	CD8+CD56+ αβ-T-LGL leukemia
	vascular mammary skin lesion	γδ-T	[130]	
	psoriasis	γδ-T	[50]	
	allergic skin involvement	γδ-T; NK	[58, 83, 130]	
autoimmune disorders (neuropathies)	multiple sclerosis (MS)	αβ-T	[94, 131]	[131] is a case of CD8+CD56+ αβ-T-LGL leukemia
	paraneoplastic neuropathy and peripheral neuropathy	T; NK	[58, 67, 83, 132, 133]	
autoimmune disorders (muscular and glandular)	myositis and other musculoskeletal symptoms	T; NK	[58, 136]	
	Sjögren syndrome	αβ-T; γδ-T	[52, 126, 129, 137, 138]	
	autoimmune thyroiditis (Hashimoto's disease)	αβ-T; γδ-T	[50, 52, 94, 129, 138]	
	autoimmune polyglandular syndrome (APS)	γδ-T	[138]	
	endocrinopathy, Grave's disease (hyperparathyroidism) and Cushing's syndrome	αβ-T	[52, 94]	
autoimmune disorders (other connective tissue disorders)	systemic lupus erythematosus (SLE)	αβ-T	[94, 129, 139]	
	Behçet disease	αβ-T	[140]	
	uveitis and celiac disease	αβ-T	[141]	
other malignancies, transplantations and genetic disorders	other malignancies (including thyroid, lung, liver, colon-rectal, prostate, testicular, melanoma, basal cell carcinoma)	αβ-T; γδ-T;	[50, 52, 94, 150, 151]	
	bone marrow and solid organ transplantation	T	[153, 154]	
	Turner syndrome	T	[152]	