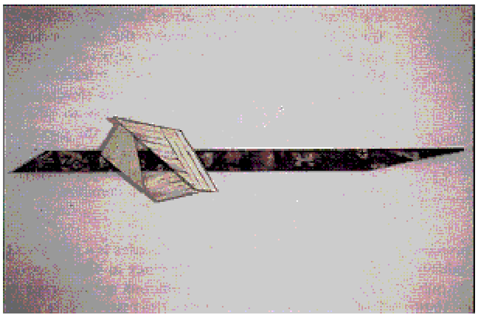


Kirk Ke Wang. Scale (1992). Mixed media, 18" x 72".

Large Granular Lymphocyte Leukemia

Thierry Lamy, MD, and Thomas P. Loughran, Jr, MD

The distinctive clinical and biological characteristics of large granular lymphocyte leukemia are reviewed.

Background: *Clonal diseases of large granular lymphocyte (LGL) disorders can arise from a CD3+ T-cell lineage or from a CD3– NK-cell lineage. CD3+ LGL leukemia is the most frequent form of LGL leukemia and is a distinct entity by FAB and REAL classifications.*
Methods: *The clinical course, biological features, and recent data on pathogenesis of CD3+ LGL leukemia are reviewed. The spectrum of differential diagnosis is described.*
Results: *T-LGL leukemia affects elderly people. Approximately 60% of patients are symptomatic; recurrent infections secondary to chronic neutropenia, anemia, and rheumatoid arthritis are the main clinical features. The most common phenotype is CD3+, CD8+, CD57+. Clonality is detected by clonal rearrangement of the T-cell receptor gene. Clinical and molecular remission can be obtained with oral low-dose methotrexate.*
Serologic findings show frequent reactivity to the BA21 epitope of HTLV-I env p21e, suggesting that a cellular or retroviral protein with homology to BA21 may be important in pathogenesis. Clonal expansion may be facilitated by IL-12 and IL-15 lymphokines. Constitutive expression of Fas ligand by leukemic LGLs support the hypothesis that leukemic cells arise from antigen-activated cytotoxic T cells. Leukemic LGLs express a multidrug-resistance phenotype that could partly explain the chemoresistance observed in aggressive cases.
Conclusions: *CD3+ LGL leukemia is a distinct lymphoproliferative T-cell disorder with specific clinicobiological aspects. The clinical spectrum of LGL proliferations is wide and immunophenotypic, and genotypic studies are needed to establish the diagnosis.*

Introduction

Large granular lymphocytes (LGLs) are a morphologically distinct lymphoid subset comprising 10% to 15% of normal peripheral blood mononuclear cells. LGLs can be classified into two major lineages: CD3+ LGLs, which represent in vivo activated cytotoxic T cells, and CD3– natural-killer (NK) LGLs, which mediate nonmajor histocompatibility complex (MHC)-restricted cytotoxicity. A syndrome characterized by the proliferation of LGLs associated with neutropenia was initially reported in 1977,[1] and several studies have been published since then on LGL proliferation disorders.[2-5] Until recently, a certain confusion remained in the literature due to the variety of terms used to describe this entity. We proposed the term *LGL leukemia* for this disorder based on demonstration of tissue invasion by LGLs of the marrow, spleen, and liver.[6] The French-American-British (FAB) classification recognized LGL leukemia as one of four subgroups of chronic T-lymphoid leukemias.[7] In 1993, we proposed that LGL leukemias could be further classified into T-LGL leukemia and NK-LGL leukemia, depending on the cell lineage of the leukemic cells.[2] Most recently, the Revised European-American Lymphoma (REAL) classification has recommended that LGL leukemia be a distinct entity classified in the peripheral T-cell and NK-cell neoplasms.[8]

In this article, we describe the recent developments in the clinical and biological features of CD3+ T-LGL leukemia, and the differential diagnosis is reviewed. The natural history, pathogenesis, and therapeutic aspects of this disease are also presented.

Clinical and Biological Features of CD3+ LGL Leukemia

This T-cell type of LGL leukemia represents 85% of the LGL leukemias. The usual patient characteristics are shown in Table 1. The disease has no specific predilection for either men or women, and it affects principally elderly people with a median age of 60 years (range: 4 to 88 years). Only 10% of the patients are younger than 40 years of age, and pediatric cases rarely have been reported. Approximately one third of patients are asymptomatic at the time of diagnosis. The initial symptoms are related to neutropenia and include fever with recurrent bacterial infections. These infections typically involve the skin, oropharynx, and perirectal areas, but severe sepsis or pneumonia can also occur. Opportunistic infections are uncommon, and fatigue or B symptoms (fever, night sweats, weight loss) are observed in 20% to 30% of cases. The physical examination reveals the presence of mild to moderate splenomegaly in 20% to 50% of cases and hepatomegaly in 20%. Lymphadenopathy is rare. Bone marrow involvement is a common feature in T-LGL leukemia.

Feature	Percentage of Cases
Recurrent infections	20 - 40%
B symptoms	20 - 30%
Splenomegaly	20 - 50%
Hepatomegaly	1 - 23%
Lymphadenopathy	1 - 23%

Data on two series of 128 and 68 patients.,[2,3]

Table 1. – Clinical Features of CD3+LGL Leukemia

An association with other diseases is a prominent feature of this lymphoid malignancy in 40% of cases. The associated comorbid conditions are reported in Table 2. Rheumatoid arthritis (RA) is the most common associated disease, occurring in approximately 25% of patients.[2,3,9] T-LGL leukemia patients with RA resemble patients with Felty's syndrome (neutropenia, RA, and splenomegaly),[10] and the articular manifestations of typical Felty's syndrome and RA-associated T-LGL leukemia are indistinguishable. The prevalence of LGL leukemia in Felty's syndrome is probably underestimated.[11]

Commonly Associated	Rarely Associated (<5%)
Rheumatoid arthritis (25%)	Myelodysplasia
Anemia (Hb <8 g/dL) (20%): pure red-cell aplasia hemolytic anemia nonregenerative anemia	Solid tumors Monoclonal gammopathy of unknown significance Multiple myeloma Endocrinopathy Hodgkin's disease Non-Hodgkin's lymphoma Hairy cell leukemia Idiopathic thrombocytopenic purpura Amegakaryocytic purpura Posttransplantation Thymoma Connected tissue diseases other than rheumatoid arthritis - Systemic lupus erythematosis - Scleroderma

Table 2. -- Associated Comorbid Conditions in CD3 +LGL Leukemia

Increased numbers of cells with a similar phenotype to leukemic cells have been observed in the blood or synovial fluid of patients with RA.[12] The onset of RA compared with that of LGL leukemia is variable from one patient to another. In some cases, the clonal LGL proliferation may precede the development of RA by several years, whereas the two diseases are simultaneously diagnosed in other cases. We and others recently reported that patients with LGL leukemia and RA have the same high frequency of DR4 haplotype as patients with Felty's syndrome -- 90% and 86%, respectively.[13,14] These data suggest that Felty's syndrome and LGL leukemia associated with RA have a similar immunogenetics basis.

LGL leukemia can coexist with other hematologic malignancies of lymphoid- or myeloid-derived clones. Monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma associated with LGL leukemia have recently been described but without an understandable relationship between the two diseases.[3,15] Several cases of myelodysplasia have been reported based on morphologic evidence of trilineage dysplasia on bone marrow, which is associated in some cases with 5q– cytogenetic abnormalities. Expansion of CD3+, CD57+ lymphocytes are frequently observed after bone marrow transplantation.[16] This may reflect either differentiation steps during reconstitution of the immune system or an activation process due to graft-versus-host disease or cytomegalovirus infection.[17] However, clonal CD3+ LGL proliferation can be observed after organ transplantation (T.P.L., Jr, unpublished data, 1997).

Hematologic Features

The diagnosis of LGL leukemia is initially suspected on the basis of persistent periphral blood lymphocytosis with the characteristics of LGLs. These cells are identified by their morphology and phenotype. They are large (15 to 18 microns), have abundant cytoplasm containing typical azurophilic granules, and have a reniform or round nucleus (Fig 1). The normal LGL count ranges from 200 to 400 cells/µL. Most patients have more than 2×10^9 LGL/L, whereas the lymphocytosis is modestly increased (median = 8×10^9/L). Careful examination of the peripheral blood smear is required in cases of normal lymphocytes counts. However, cytoplasmic granules may occasionally be absent despite a typical LGL phenotype.

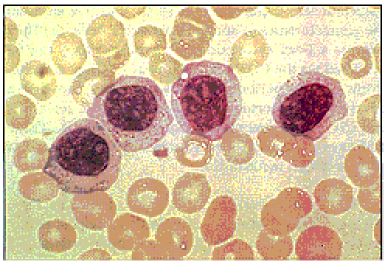


Fig 1. – Characteristic cytologic features of T-LGL leukemia. Peripheral blood smear shows typical LGLs with intracytoplasmic granules.
Photo courtesy of Bruce Cheson, MD.

Table 3 summarizes the hematologic findings of T-LGL leukemia. Most patients present with chronic neutropenia. Adult-onset cyclic neutropenia is sometimes associated with T-LGL leukemia.[18] The mechanism of neutropenia is not fully elucidated. A direct effect of abnormal LGLs on myeloid precursors (colony-forming units granulocyte/macrophage [CFU-GM]) has rarely been demonstrated. Although diffuse bone marrow infiltration by LGL is common, no correlation has been shown between the degree of neutropenia and marrow infiltration. An autoimmune process is not excluded since antineutrophil antibodies are frequently increased. The recent demonstration of constitutive expression and excretion of Fas ligand by leukemic LGLs implicates Fas ligand as a possible pathogenetic mechanism in neutropenia.[19,20]

Commonly Associated	Rarely Associated (<5%)	
Neutropenia	ANC $<1.5 \times 10^9$/L	80%
Severe neutropenia	ANC $<0.5 \times 10^9$/L	45%
LGL counts:	$<1 \times 10^9$/L $1 - 4 \times 10^9$/L $>4 \times 10^9$/L	8% 40% 52%
Lymphocytosis	$>5 \times 10^9$/L	50%
Anemia	Hemoglobin <11 g/dL	48%
Thrombocytopenia	Platelets $<150 \times 10^9$/L	20%
LGL bone marrow infiltration		>70%

Table 3. -- Hematologic Features of CD3+LGL Leukemia

Anemia is frequently observed with several different underlying mechanisms: Coombs' positive autoimmune hemolysis, pure red-cell aplasia, or decreased erythroid marrow progenitors. Thrombocytopenia also occurs frequently. Specific inhibition of CFU-E, BFU-E, or CFU-MK by leukemic LGLs has been reported in patients with pure red-cell aplasia or amegakyocytic purpura, respectively. Conversely, cytopenias have been observed in association with positive Coombs' tests and antiplatelet antibodies. Thrombocytopenia is usually moderate, but transfusion-dependent anemia is seen in approximately 20% of patients.

Serologic Findings

Immune abnormalities are frequently observed in T-LGL leukemia (Table 4). Rheumatoid factor, the most common abnormality, is detected in 60% of patients. Antinuclear antibody is also positive in 40% of patients.[2,3] Serum protein electrophoresis usually shows polyclonal hypergammaglobulinemia, and monoclonal gammopathy of either IgG-kappa or IgG-lambda subtype has been reported.[3] Antineutrophil antibodies are frequently positive, but their pathogenetic significance is not well established as these patients often have increased levels of circulating immune complexes.

Feature	Percentage of Cases
Rheumatoid factor	60%
Antinuclear antibody	40%
Polyclonal hypergammaglobulinemia	10-40%
Monoclonal gammopathy	8%
Circulating immune complexes	55%
Antineutrophil antibody	40%
Positive Coombs' test	15%

Table 4. -- Serologic Findings in CD3+LGL Leukemia

Immunologic Classification

LGL expansions show a mature postthymic phenotype with a degree of membrane heterogeneity. The vast majority of T-LGL leukemia shows a CD3+, TCR alpha beta+, CD4–, CD8+, CD16+, CD57+ phenotype.[2,4,5] Leukemic LGLs also constitutively express CD2, CD45 RA, and interleuken (IL)-2R beta (p75, CD122) but not IL-2R alpha (p55, CD25). CD56+ is rarely expressed. Some cases express CD4 antigen with or without coexpression of CD8. A CD4–, CD8– phenotype has also been rarely reported. LGL leukemic cells express perforin, a component of the cytoplasmic granules found only in NK cells or cytotoxic T lymphocytes. Some authors have proposed an immunologic classification, but the prognostic implication of this remains controversial.[21] Nevertheless, it seems that CD3+, CD56+ subtypes have an aggressive clinical behavior.[22]

The clonal nature of LGL leukemia is most easily assessed by molecular studies of the T-cell receptor (TCR). The analysis of TCR beta and/or TCR gamma chain gene rearrangement is commonly assessed by Southern analysis. The sensitivity is increased by using specific primers of TCR-V gamma or TCR-V beta with polymerase chain reaction technique. Murine monoclonal antibodies reactive with human TCR variable region are now commercially available to study the TCR-V beta repertoire. One study suggested a restricted use of V beta 13.1 region in leukemic LGL.[23] A few cases of CD3+, TCR gamma delta+ have been reported, and they show a similar clinical pattern as TCR alpha beta+ cases.[24] Chromosome abnormalities involving chromosomes 8 and 14 have been detected, which further demonstrates the clonal nature of this disease.[6]

Etiology

The etiology of LGL leukemia is not known. However, it is hypothesized that the expansion of CD3+ leukemic cells requires several steps. The cells show all the characteristics of antigen-activated T cells: (1) They express a T-cell cytotoxic phenotype, (2) they can be activated via the CD3, CD16 pathway, (3) they constitutively express perforin, (4) in some cases, they use a restricted V beta repertoire, suggesting antigenic selection, and (5) they constitutively express Fas ligand. These data suggest that an initial step in LGL expansion is an antigen-driven mechanism.

We have investigated the role of human T-cell leukemia virus (HTLV) infection in this model of pathogenesis. We detected HTLV-II in one patient with LGL leukemia.[25] However, most patients are not infected with prototypical HTLV-I/II.[26] Serologic findings in T-LGL leukemia are suggestive of infection with HTLV. Sera from these patients react with recombinant HTLV-I/II *env* p21e but not with gp46 *env* protein. Epitope mapping studies have shown that reactivity against *env* p21e is directed at the BA21 epitope. We hypothesize that a cellular or retroviral protein having homology to BA21 may be important in the pathogenesis of LGL leukemia.

The persistence and proliferation of LGL could be due to the stimulatory effect of various cytokines. Recent data suggest that IL-12 and IL-15 may be important in the leukemogenesis. IL-12 increased the proliferation of anti-CD3 monoclonal antibody prestimulated LGL and upregulation of IL-12 mRNA and IL-12 receptors is observed after LGL activation.[27,28] IL-15 stimulates LGL and mediates this activity through the beta and gamma chains of IL-2 receptor.[29]

Prognosis and Therapy

T-LGL leukemia is usually a chronic disease. The first large series published in the literature reported 26 deaths among 151 patients after a mean follow-up of 23 months.[30] A recent study of 68 patients reported a median survival superior to 10 years.[3] Some patients may remain asymptomatic for more than five years. Patients with uncomplicated cytopenia are followed until symptomatic progression. However, most of the patients require therapy (69% in the study by Dhodapkar et al[3]). The indications for therapy are listed in Table 5. It is emphasized that standard therapy is undefined. The main indication for treatment is recurrent infection due to severe neutropenia. Splenectomy is usually ineffective in correcting neutrophil counts and may increase circulating LGL cells.

Indications	Therapy
Neutropenia with associated infections	Methotrexate ± prednisone G-CSF/GM-CSF Cyclosporine A
Anemia	Cyclophosphamide ± prednisone Chlorambucil
Splenomegaly (± ITP, HA)	Splenectomy Methotrexate ± prednisone
Aggressive disease	Methotrexate ± prednisone Combination chemotherapy Fludarabine Allogeneic bone marrow transplantation
ITP = idiopathic thrombocytopenic purpura HA = hemolytic anemia	

Table 5. -- Treatment of CD3+LGL Leukemia

The benefit of hematopoietic growth factors is controversial. In the few cases in which GM-CSF or G-CSF has been used, the responses are usually partial and transient.[31] Cyclosporin A has occasionally led to good responses, but its toxicity remains a problem for long treatment.[32] Some patients respond to prednisone alone with an increase in neutrophil count but also with persistence of LGL clone. We initially reported the efficacy of oral low-dose methotrexate in LGL leukemia with a complete remission in 50% of cases.[33] A molecular remission was observed in three out of five patients who achieved complete remission. Pure red-cell aplasia or symptomatic anemia has been primarily treated with chemotherapy such as cyclophosphamide, chlorambucil, or prednisone. Cyclophosphamide ± prednisone is associated with a longer duration of response than prednisone alone.[3] Overall response to initial therapy is approximately 66%, and the median duration of response is 32 months. In multivariate analyses, the risk factors associated with poor clinical outcome were fever at diagnosis, low percentage of CD57+ cells, and low peripheral LGL counts.[30] In another study, severe neutropenia or B symptoms were associated with a lower probability of complete remission.[3] Spontaneous remission has been documented very rarely.[3]

Aggressive cases of T-LGL leukemia are usually treated with combination chemotherapy (CHOP-like regimen). The response rate is poor, and most patients die within one year of the start of treatment. The behavior of these aggressive cases is similar to that of NK-cell lymphomas, which are now recognized as a lymphoid malignancy with a particularly poor prognosis. One possible reason for the adverse outcome is that LGL leukemic cells, like their normal counterparts (NK or T-cytotoxic phenotype cells), constitutively express high levels of P-glycoprotein, the product of the multidrug resistance gene (MDR1).[34-37]

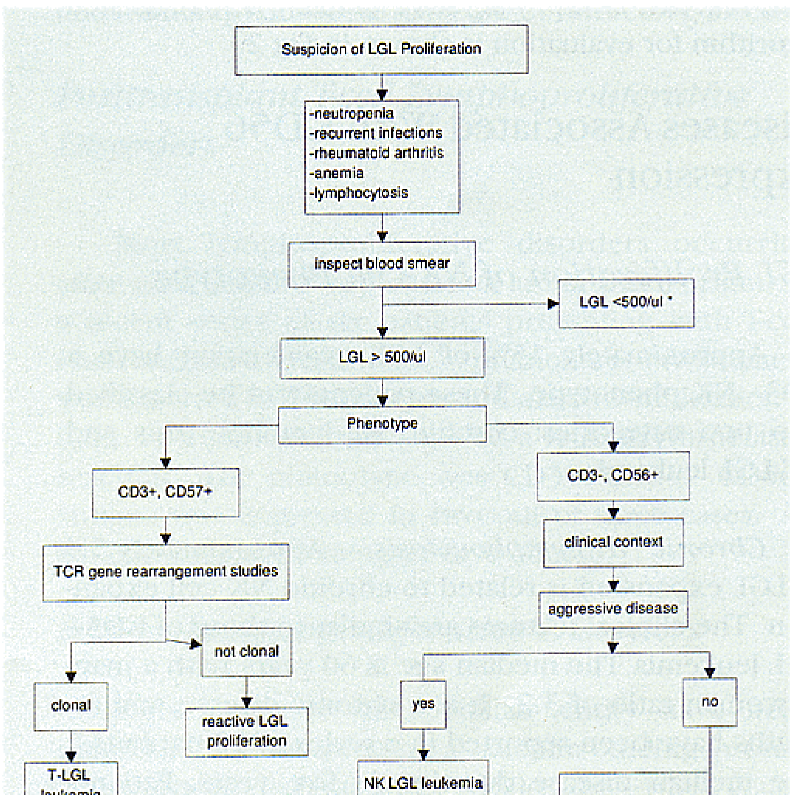
We recently reported three cases of aggressive non-nasal NK lymphoma.[38] Two patients displaying MDR1 phenotype were refractory to combined chemotherapy regimen, and they died rapidly after the diagnosis. The third patient was MDR1– and responded favorably to chemotherapy and remains in complete remission. We have found that chronic LGL leukemias express relatively high levels of P-glycoprotein[39] and also P110, another protein implicated in drug resistance (T.L., unpublished data, 1997). The evolution from chronic to aggressive chemoresistant LGL leukemia has been documented, and MDR phenotype may explain treatment failure in these cases.[40] Interestingly, we have observed patients who were resistant to combination chemotherapy including anthracyclines but who responded to methotrexate, a drug not involved in P-glycoprotein transport. Few data exist on the efficacy of fludarabine, but complete remission has been reported in a patient treated with fludarabine as second-line therapy.[3] Allogeneic bone marrow transplantation should be considered for young patients who have a sibling donor and who have refractory disease.

Differential Diagnosis

The differential diagnosis of LGL leukemia should be considered in two different contexts: diseases associated with CD56 expression and those associated with reactive LGL proliferation (Table 6). A suggested algorithm for evaluation is shown in Fig 2.

CD56+ Cell Proliferative Diseases
LGL proliferative of NK-cell phenotype
Chronic NK lymphocytosis
NK-LGL leukemia
NK-cell lymphoma
NK-like T-cell lymphoma
Gammatheta T-cell lymphoma
Posttransplant T-cell lymphoproliferative disorders
S-100+ T-cell lymphoproliferative disorders
CD56+ acute leukemia
Reactive LGL Proliferation
Solid Tumors
Connective tissue diseases
Hemophagocytosis syndrome
Idiopathic thrombocytopenic purpura
Non-Hodgkin's lymphoma
Viral infections

Table 6. – Differential Diagnosis of T-LGL Leukemia



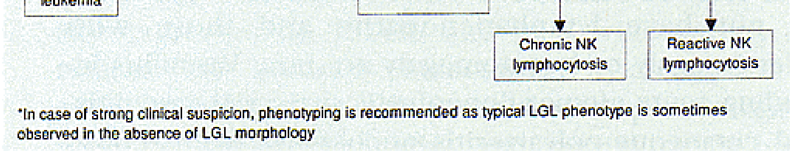


Fig 2. -- A suggested algorithm for evaluation of LGL leukemia.

Diseases Associated With CD56 Expression

LGL Proliferation of NK-Cell Phenotype

Approximately 15% of LGL proliferation have a CD3– NK phenotype. These patients can be classified into two categories: chronic NK lymphocytosis and NK-LGL leukemia.

Chronic NK Lymphocytosis -- Approximately 5% of LGL expansion is related to chronic NK cell expansion. The clinical features are similar to those of CD3+ LGL leukemia. The median age is 60 years with a man-to-woman ratio of 3.2. It is a chronic disease, and no deaths have been reported in a series of 10 patients.[41] The median disease duration is five years. Patients do not have lymphadenopathy, and those with splenomegaly or hepatomegaly are rare. Vasculitis including acute glomerulonephritis, urticarial vasculitis, and cutaneous polyarteritis nodosa has been reported,[41] and pure-cell aplasia and mild thrombocytopenia have been observed. The severity of neutropenia is less than that in T-cell LGL leukemia. The median absolute number of NK cells is 2.3 x 10^9/L, and the main phenotype is CD2+, CD3–, CD4–, CD8–, CD16+, CD56+. CD57 is usually weakly expressed.

Different antigens expressed on NK cells subsets and belonging to the 58 Kd molecular family have been recently described.[42] Monoclonal antibodies EB6 and GL183 recognize two of these antigens. Four different subsets of normal NK cells can be distinguished using these monoclonal antibodies. Most patients with NK-cell lymphocytosis have a restricted NK phenotype, with the NK expansion representing one of these four subsets.[43] Since this is an indolent disease, therapy is usually not needed. Severe neutropenia has been treated with prednisone ± cyclophosphamide or methotrexate. It is not clear whether chronic NK lymphocytosis represents a benign disorder or a chronic phase of NK-LGL leukemia. Follow-up studies assessing clonality in NK lymphocytosis are needed to demonstrate any clonal progression during a transformation in NK-LGL leukemia.[40]

Viral infections have been implicated in the pathogenesis of NK lymphocytosis. A series from Italy reported some evidence for viral infection in 13 of 18 patients.[44] No evidence of Epstein-Barr virus (EBV) was found in our study,[45] and HTLV-I/II was not detected in a French series of 27 patients with NK lymphocytosis.[46] We recently discovered that sera from patients with chronic NK lymphocytosis react to an envelope protein of HTLV-I/II. Using epitope mapping, we found that seroreactivity was detected at the specific BA21 epitope of this transmembrane envelope protein.[47] A protein having homology to BA21 may be important in the pathogenesis of NK lymphocytosis as well as of T-LGL leukemia.

NK-LGL Leukemia -- The clinical and biological features of NK-LGL leukemia are presented in Table 7. The clinical presentation is more aggressive in NK-LGL leukemia than in CD3+ leukemia. Patients are younger (median age = 39 years), and the initial presentation includes B symptoms and hepatosplenomegaly. Rheumatoid arthritis has never been observed.[2,48] Most patients have bone marrow infiltration, sometimes with marrow fibrosis, and some patients have an involvement of the gastrointestinal tract. Ascites with LGL infiltration of peritoneal fluid has been reported[49] as well as involvement of the cerebrospinal fluid with LGL. Anemia and thrombocytopenia occur more frequently in NK-LGL than in CD3+ cases, and neutropenia is usually moderate. Absolute LGL counts are higher than those in T-cell LGL leukemia, with many patients reaching more than 10 x 10^9 LGL/L. The usual phenotype is CD3–, TCR alpha beta–, TCR gamma delta–, CD4–, CD8+, CD16+, CD56+. CD57 is variably expressed. These cases of CD3– LGL leukemia do not show any rearrangement of TCR genes. Cases described in Asia have been associated with clonal cytogenetic abnormalities.[50]

Clinical Features	**Biological Findings**
Marrow infiltration 100%	Neutropenia (ANC <2 x 10^9/L) 50%
Splenomegaly 90%	Severe neutropenia (ANC <0.5 x 10^9/L) 18%
Hepatomegaly 60%	Anemia (hemoglobin <10 g/dL) 100%
Lymphadenopathy 27%	Thrombocytopenia (platelets <150 x 10^9/L) 75%
	Hyperlymphocytosis (>10 x 10^9/L) 70%
Rarely Reported:	
Gastrointestinal infiltration	
CNS involvement	
Ascites	
Idiopathic thrombocytopenic purpura	
Disseminated intravascular coagulation	

Table 7. – Clinical and Biological Features of CD3-NK-LGL Leukemia

In a study by Kawa-Ha et al,[51] EBV infection was implicated in NK-LGL leukemia in more than 50% of the cases. In situ hybridization analyses have shown EBV RNA within the LGLs. Using immunoblotting, EBV nuclear antigen 1 can be detected in leukemic cells. These data suggest that EBV may be directly involved in LGL cell transformation similar to EBV-associated B-cell lymphoma.[51]

Most patients have a severe and refractory evolution. In our review, nine of 11 patients died within two months after diagnosis.[2] Multiorgan failure associated with coagulopathy is the main cause of death. Combination chemotherapy is ineffective, and long-term remission occurs rarely. The MDR phenotype may be implicated in drug resistance in these cases.

NK-cell Lymphoma

The spectrum of NHL is not restricted to B or T lineage but now includes non-T and NK-cell lymphoid malignancies.[8,52] NK-cell lymphoma is a heterogeneous disease. Most cases have been described in Asia, involve the nasopharynx, and are related to EBV infection.[52] Some sporadic non-nasal cases have been described in Europe and North America.[38] The phenotype is variable (usually CD3–, CD56+). The cells are intermediate or large in size with features of pleiomorphic cell lymphoma. The median overall survival is 11 months, with a longer survival in localized cases compared to cases with multiorgan involvement.

NK-like T-cell Lymphoma

Aggressive lymphomas of T-LGL have recently been described. All the patients presented with B symptoms and marked hepatosplenomegaly. Bone marrow infiltration and peripheral blood involvement by neoplastic large lymphocytes of CD3+, CD56+ phenotype are observed. The prognosis is very poor.[53] These patients probably have a similar disease to that described previously as an aggressive CD3+, CD56+ variant of LGL leukemia.[22]

Gamma Delta T-cell Lymphoma

This aggressive disease has been recognized as a distinct entity.[54] Patients are young men who present with hepatosplenomegaly but without lymphadenopathy or peripheral blood lymphocytosis. Thrombocytopenia and anemia are common. The phenotype is CD3+, gamma delta+, CD16+, CD56+. Isochromosome 7q has been observed in some patients. Despite combined chemotherapy, most patients die of refractory disease.

Posttransplant T-cell Lymphoproliferative Disorders

Most lymphoproliferative disorders occurring after solid organ transplantation are of B-cell origin. In a recent series of six patients presenting with T-cell non-Hodgkin's lymphoma,[55] pulmonary involvement was reported in five patients and marrow infiltration in four. Five patients also showed a leukoerythroblastic reaction. The phenotype was CD3+, CD8+. CD56+ antigen was expressed in two out of three cases. All patients displayed an aggressive course.

S-100+ Lymphoproliferative Disorders

Eight cases of this peculiar entity have been reported.[56] S-100 protein, a calcium-binding protein consisting of two fractions, S-100 alpha and S-100 beta, is usually expressed on T cells and in a wide variety of tumors. This disease is characterized by an aggressive clinical behavior. Patients present with splenomegaly, with no lymphadenopathy, and usually with high white blood cell counts. The phenotype of the leukemic cells is CD4–, CD8±, CD56+, S-100 beta+. Genotypic studies demonstrated beta-chain TCR gene rearrangement. Combined chemotherapy is often ineffective.

Acute Leukemia

Unusual cases of CD3–, CD16+, CD56+ or CD3+, CD16+ phenotype have been reported in acute lymphoblastic leukemia. The blasts cells exhibit FAB L2 blast morphology. Some cases of CD33+, CD56+ myeloid/NK-cell leukemia have also been described.[57]

Diseases Associated With Reactive LGL Proliferation

Secondary LGL expansions have been reported in many clinical situations. The cells can be CD3+, and TCR genes are in germline configuration. They may also display an NK-cell phenotype. Viral infections (EBV, cytomegalovirus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus), connective tissue disease, idiopathic thrombocytopenia purpura, various skin disorders, and hemophagocytosis syndrome are the main nonmalignant disorders potentially associated with reactive LGL expansion.[2,5,58,59] Myelodysplasia, non-Hodgkin's lymphoma, and solid tumors are sometimes associated with increased NK cells in peripheral blood.[58]

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