T- CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

Definition

- T-LGL is a heterogeneous disorder characterized by a persistent (>6 months) increase in the number of peripheral blood large granular lymphocytes, usually between 2-20 x 10^9/L, without a clearly identified cause

Synonyms

- T-cell chronic lymphocytic leukemia
- Tγ-lymphoproliferative disorder
- Proliferation of large granular lymphocytes
- LGL leukemia

Epidemiology

- T-LGL leukemia represents 2-3% of cases of small lymphocytic leukemia

Sites of Involvement

- T-LGL involves the PB, BM, liver, spleen
- Lymphadenopathy is very rare

Clinical Features

- Most cases have an indolent course
- Severe neutropenia with/without anemia is frequent disease feature
- 60% of pts are symptomatic at presentation
- Lymphocytosis is usually between 2-20x10^9/L
- Severe anemia due to red cell hypoplasia has been reported

Clinical Features

- Moderate splenomegaly is the main physical finding
- RA, autoantibodies, circulating immune complexes and hypergammaglobulinemia are also common

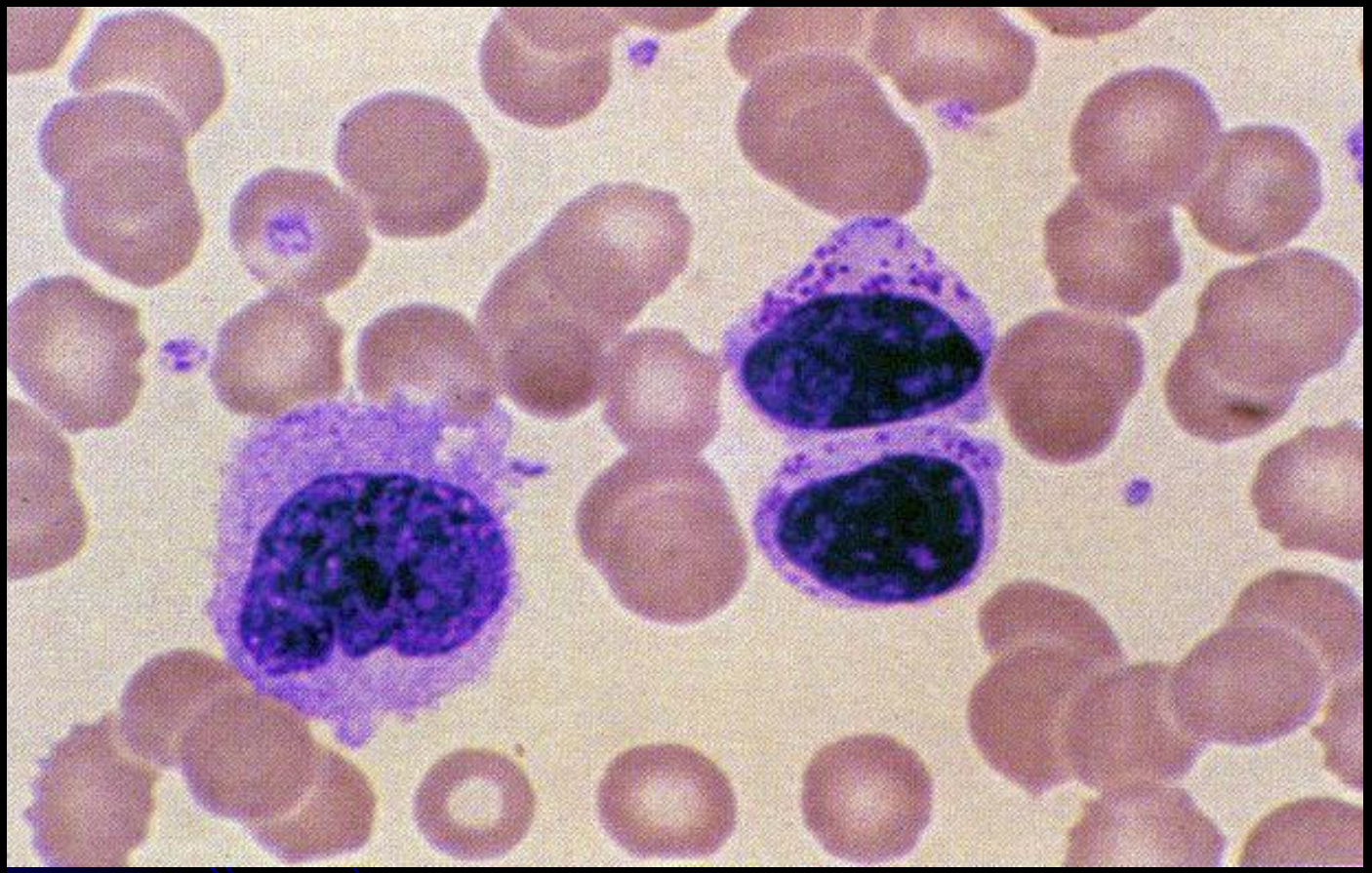
Morphology

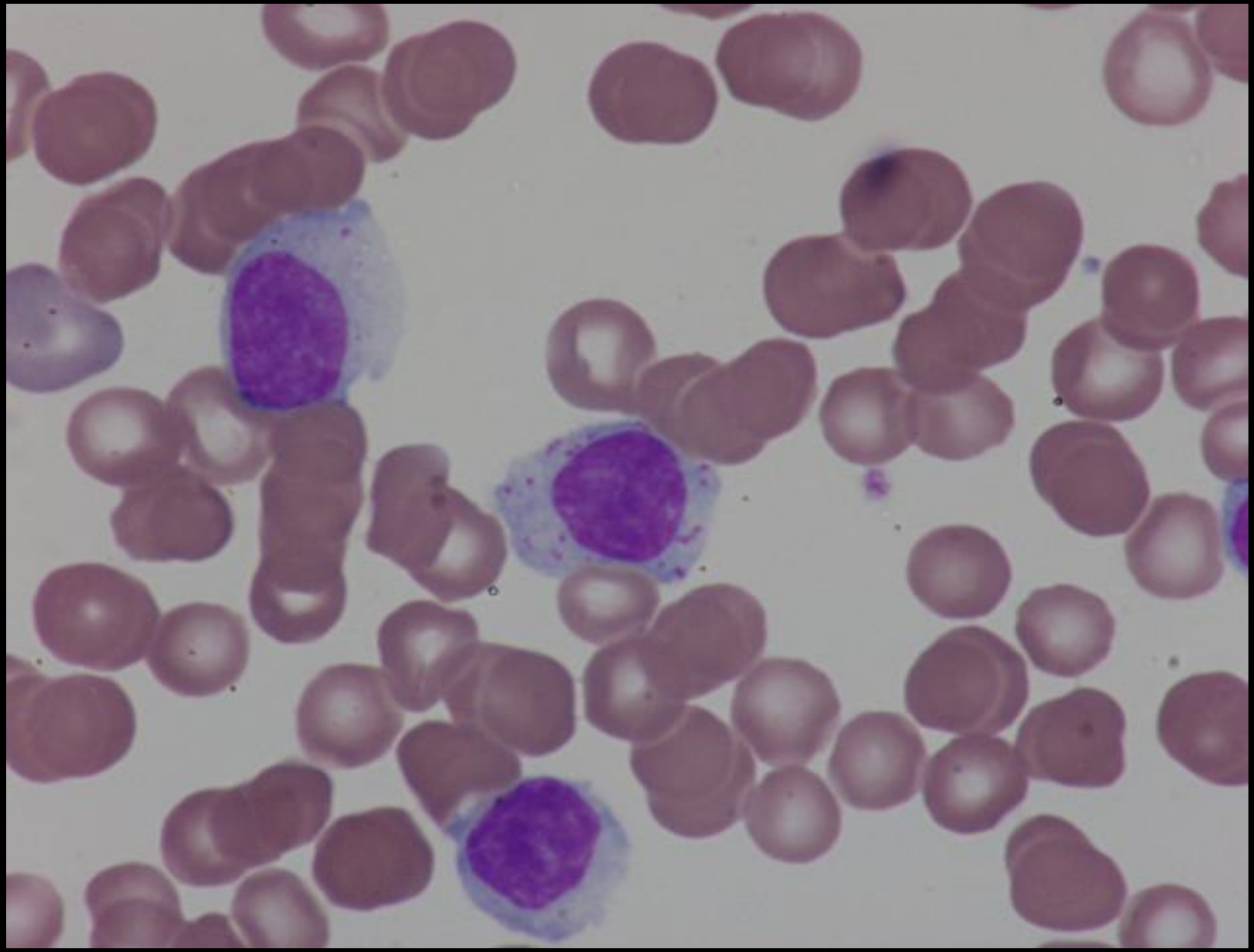
- LGL with abundant cytoplasm and fine or coarse azurophilic granules
- The granules often exhibit a characteristic ultrastructural appearance described as parallel tubular arrays
- Contain a number of proteins that play a role in cytolysis such as perforin and granzyme B

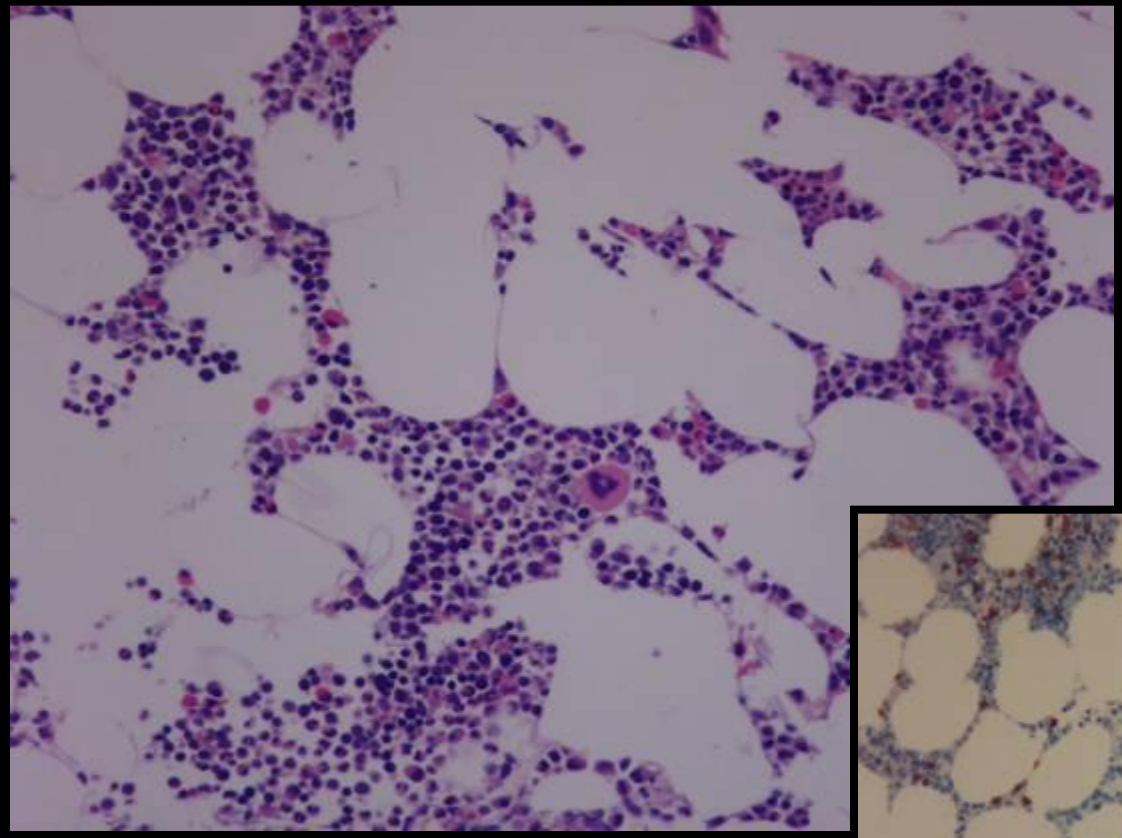
Morphology

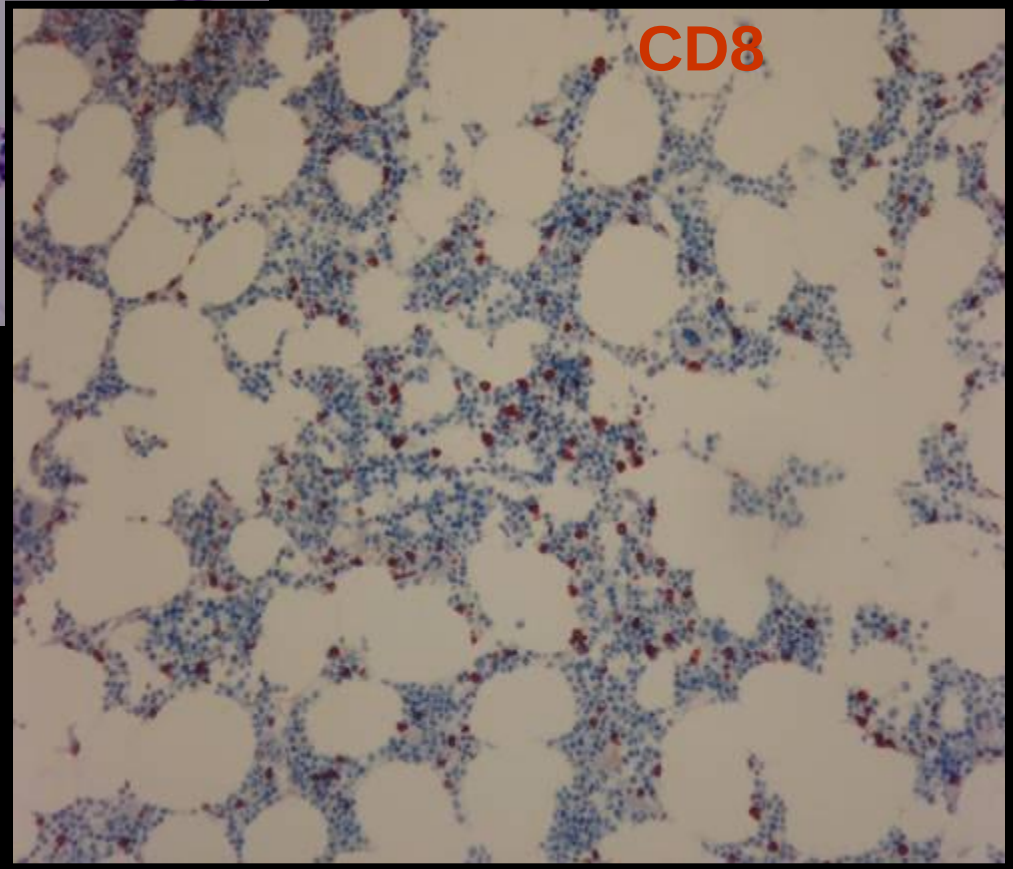
- There is no agreement on the level of lymphocytosis required for the diagnosis
- Reactive lymphocytosis often has a value $<5x10^9/L$ and T-LGL $>5x10^9/L$
- Bone marrow involvement is variable with often interstitial and rarely nodular pattern
- Lymphocytes comprise less than 50% of cellularity

T-Cell Large Granular Lymphocytic Leukemia









Bone marrow

Variant

- Cases morphologically resembling T-LGL leukemia but with a NK immunophenotype (sCD3-, TCR$\alpha\beta$-) are classified with the NK disorders

Immunophenotype

- Mature T-cell immunophenotype
- Common variant (80%):
  - CD3+, TCR αβ +, CD4-, CD8+
  - **Rare variants:**
    CD3+, TCR αβ +, CD4+, CD8-
    CD3+, TCRαβ+, CD4+ and CD8+
    CD3+, TCR γδ + (CD4 and CD8 expression not well defined)

Immunophenotype

- CD11b, CD56 and CD57 are variably expressed
- CD57 is often expressed in the common type
- TIA-1 is usually positive

Genetics

- Most cases have TCRβ chain gene rearranged and only in a minority the TCR β is in germline configuration, but have a rearrangement of TCRγ

Cytogenetics

- There is no unique karyotypic abnormalities
- Chromosomal translocations have been described in a minority of cases
- Leukemic LGLs express constitutively Fas (CD95) and Fas-ligand
- Fas ligand is found at high levels in the patient's sera
- The LGL cells, however are resistant to Fas-induced apoptosis, due to defective CD95 apoptotic pathway

Postulated Cell Origin

- CD8+ T-cell subset for the common type
- T$\gamma\delta$ lymphocytes for the rare type expressing the T-cell receptor (TCR) $\gamma\delta$

Prognosis and Predictive Factors

- Opinion varies with regard to whether all cases of T-LGL leukemia represent leukemic disorders
- For cases where the clinical course is more indolent, the possibility of clonal reactive lymphocytosis has been raised
- Morbidity is associated with neutropenia, but mortality is uncommon

Prognosis

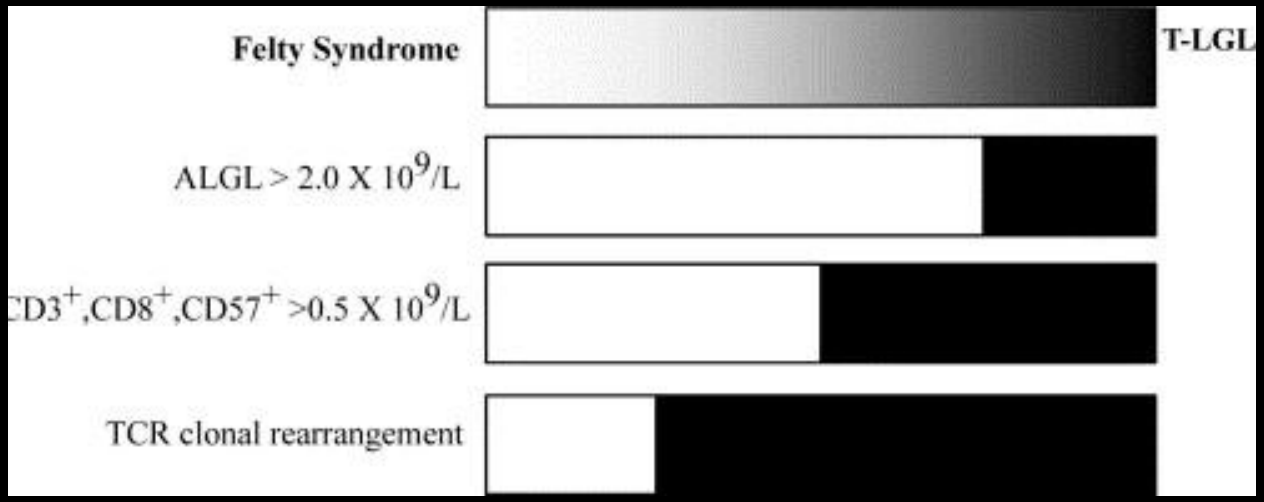
- Progression with a more aggressive course is occasionally seen
- In a minority of cases transformation to a peripheral T-cell lymphoma composed of large cells has been suggested
- Pts that require Tx may benefit from cyclosporin A, methotrexate, cyclophosphamide and steroids

Prognosis

- Other pts may benefit form pentostatin
- Splenectomy has been carried out in pts with a large spleen, but this does not correct the cytopenia

Spectrum of Disorders: Felty Syndrome, RA & LGL

Burks et al., Blood Reviews (2006) online article



- Felty syndrome (FS): neutropenia, splenomegaly, and RA
- T-LGL is distinguished from FS by the presence of T-cell clonality via TCR studies
- 25-30% of T-LGL patients have RA
- Rheumatologic associations are milder in TLGL than in FS

Spectrum of Disorders: Felty Syndrome, RA & LGL

Semenzato et al., Blood, Vol 89, No 1,1997

Table 1. Clinical Features in LDGL Patients With a Low Number of GL (<2,000/μL) as Compared With Findings Detected in Cases With Typical Disorder

	Patients With Low GL Count (<2,000/μL)		Typical LDGL Patients (>2,000/μL)	
Variable	Observed	%	Observed	%
Sex (female/male)	6/5		65/86	
Associated diseases	8/11	72.7	82/151	45.6
Systemic B symptoms	1/11	9.0	41/151	27.1
Recurrent infections	6/11	54.5	93/151	61.5
Oral ulcers	1/11	9.0	7/151	4.6
Splenomegaly	5/11	45.4	66/132	50.0
Hepatomegaly	1/11	9.0	51/151	33.7
Lymphadenopathy	0/11	0	19/132	14.3
Skin involvement	0/11	0	5/146	3.4
Therapy required	9/11	81.8	45/151	29.8
Response to therapy				
Complete	0/9	0	1/45	2.2
Partial	5/9	55.5	18/45	40.0

Normal number of peripheral blood LGL (<0.5 × 10^9/L) may be seen in 25% to 30% of cases in which the degree of bone marrow infiltration and concurrent evidence of T-cell clonality is sufficient for diagnosis.

Spectrum of Disorders: Felty Syndrome, RA & LGL

Burks et al., Blood Reviews (2006)

Table 1 Selected clinical features of TLGL, FS, and RA.[15–17,82,83]

	TLGL	FS	RA
Demographics			
M:F	1:1	1:1.5	1:2
Median age	60	60	45
Family history RA	Occasional	42%	10%
Organomegaly			
SM	20–50%	100%	12%
HM	10–20%	45%	Unusual
LAD	<5%	27%	12%
Serologic Studies			
RF	40–60%	98%	70–80%
Neutrophil IC	20%[a]	77%	64%
Extra-articular disease			
Rheumatoid nodules	Unusual	76%	53%
Leg ulcers	Unusual	25%	Unusual

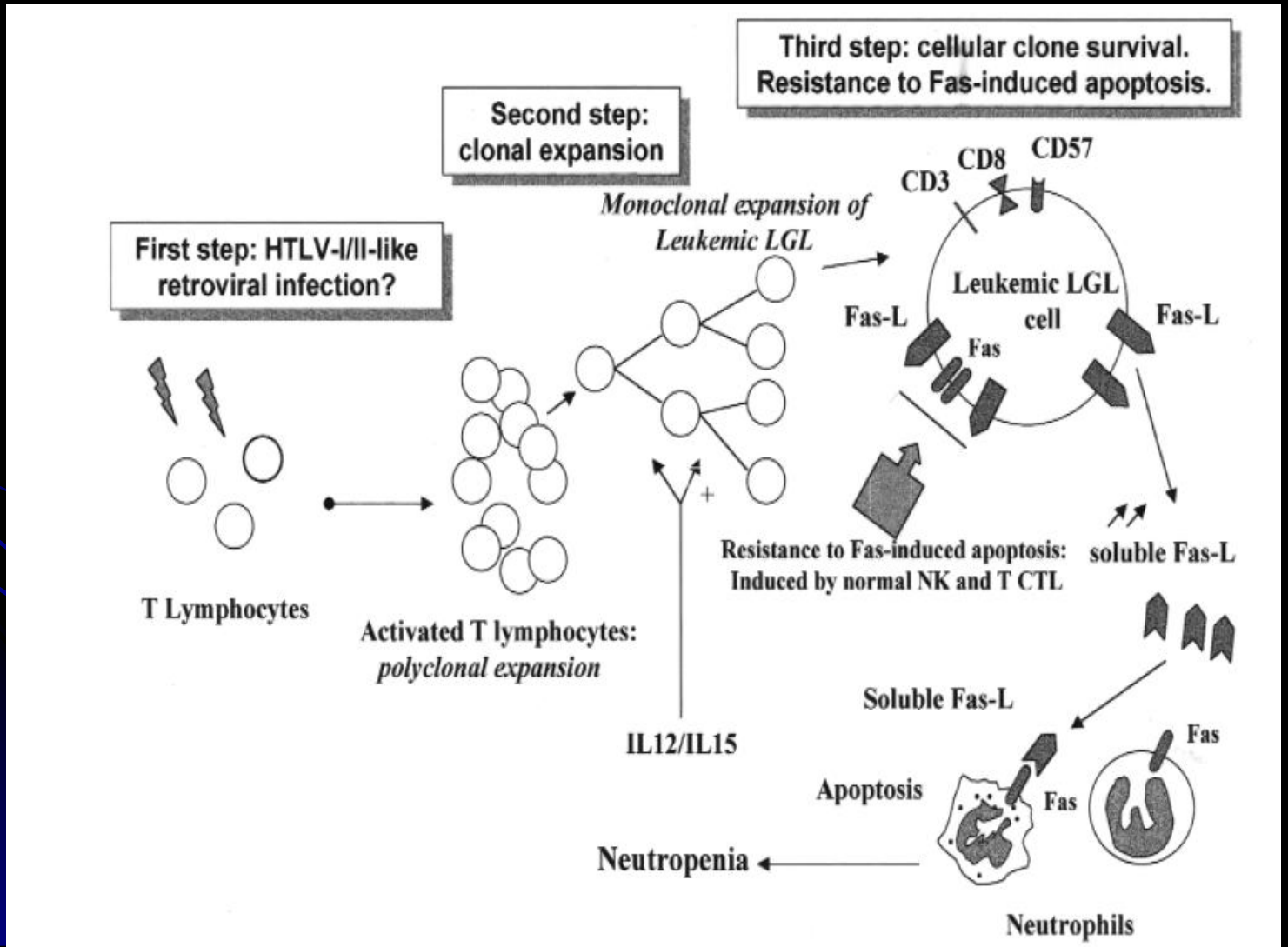
Abbreviations: RA, rheumatoid arthritis; SM, splenomegaly; HM, hepatomegaly; LAD, lymphadenopathy; RF, rheumatoid factor; IC, immune complex.

[a] Number reflects TLGL patients without RA.

- Age of onset of TLGL & FS is about 15 yrs after RA

Pathogenesis

Lamy et al., Blood Reviews (1999) 13



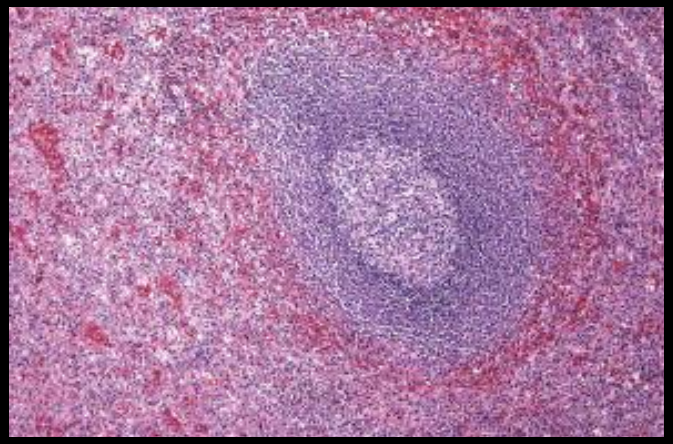
Pathogenesis

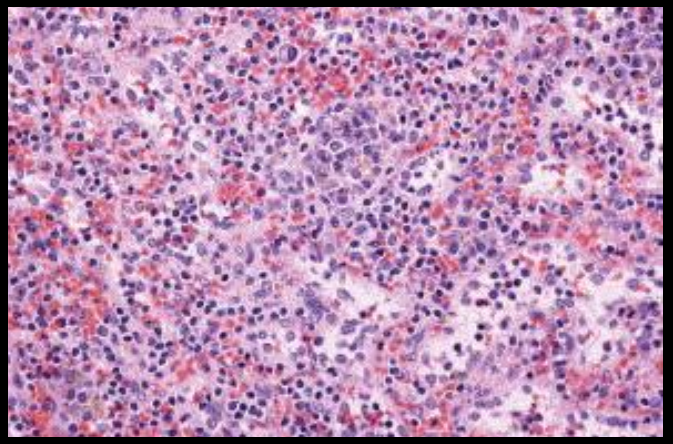
Lamy et al., Blood Reviews (1999) 13

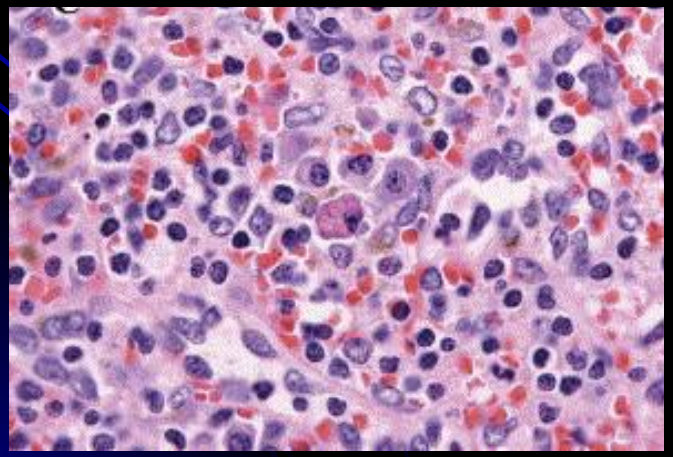
- Fas L-mediated apoptosis of neutrophils
- TNF-α & INF-γ associated myelo-suppression.
- Precipitated Immune complexes (IC) activation of neutrophils associated with increased apoptosis

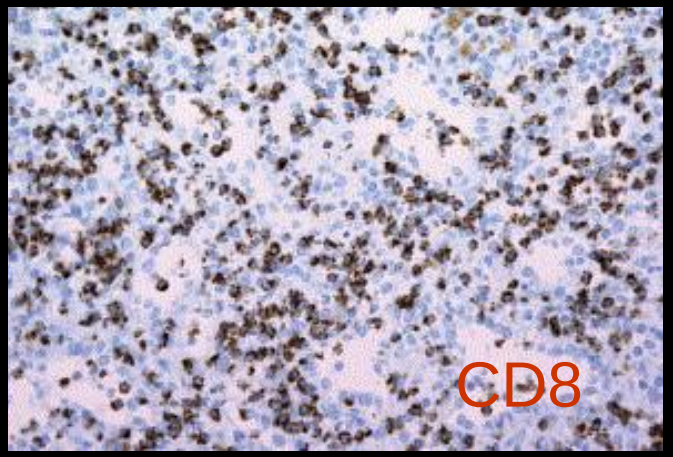
Spleen in Felty Syndrome & LGL

Burks et al., Blood Reviews (2006)









Bone Marrow Findings of Felty Syndrome vs LGL

Burks et al., Blood Reviews (2006)

- Hypercellular in both conditions
- FS: granulocyte survival defect: myeloid hyperplasia and left shifted maturation
- T-LGL: granulocyte proliferation defect: maturation arrest with myeloid hypoplasia
- Severity of myeloid proliferation defect appears to correlate with the density of lymphocytic infiltrate in the marrow
- FS may show combination of survival and proliferation defect

AGGRESSIVE NK-CELL LEUKEMIA

Definition

- NK-cell leukemia is characterized by a systemic proliferation of NK cells
- The disease has an aggressive clinical course

Synonyms

- Kiel, Lukes-Collins, Working Formulation: Not listed
- REAL: Large granular lymphocyte leukemia, NK-cell leukemia, NK-cell type
- Others: Aggressive NK-cell leukemia/lymphoma

Epidemiology

- Rare form of leukemia/lymphoma
- More prevalent among Asians than Whites
- Pts are mostly teenagers and young adults
- There is no sex predilection or sex predominance

Sites of Involvement

- Most commonly involved sites are: PB, BM, liver and spleen
- The number of neoplastic cells in the PB and BM can be limited
- NK-cell leukemia might represent the leukemic counterpart of extranodal NK/T cell lymphoma-nasal type

Clinical Features

- Pts present with fever, constitutional symptons and a leukemic blood picture
- The number of circulating leukemic cells can be low or high (a few percent to >80%)
- Anemia, neutropenia and thrombocytopenia are common
- Hepatosplenomegaly is common and lymphadenopathy
- Skin lesions are uncommon
- The disease may be complicated by coagulopathy, hemophagocytic syndrome or multiple organ failure

Clinical

- Fas ligand level is often markedly elevated
- Rare cases may evolve from extranodal NK/T-cell lymphoma or indolent NK-cell lymphoproliferative disorder

Etiology

- Little is known about the etiology
- Strong association with Epstein-Barr virus (EBV) infection
- Rare pts may manifest features of hypersensitivity to mosquito bites

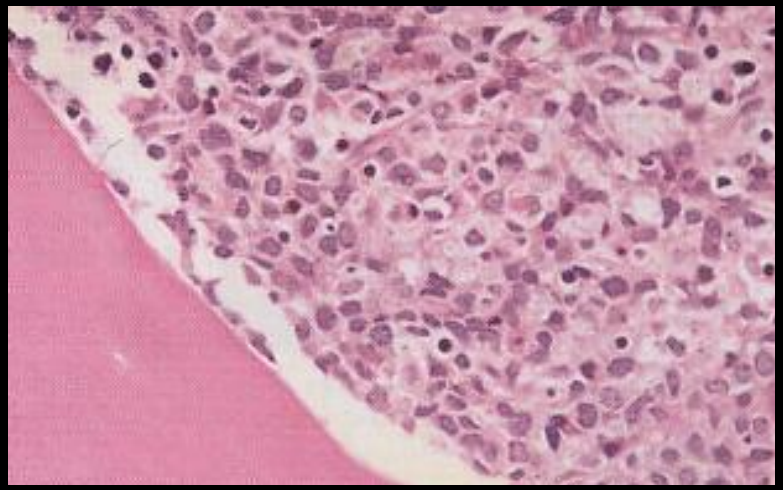
Morphology

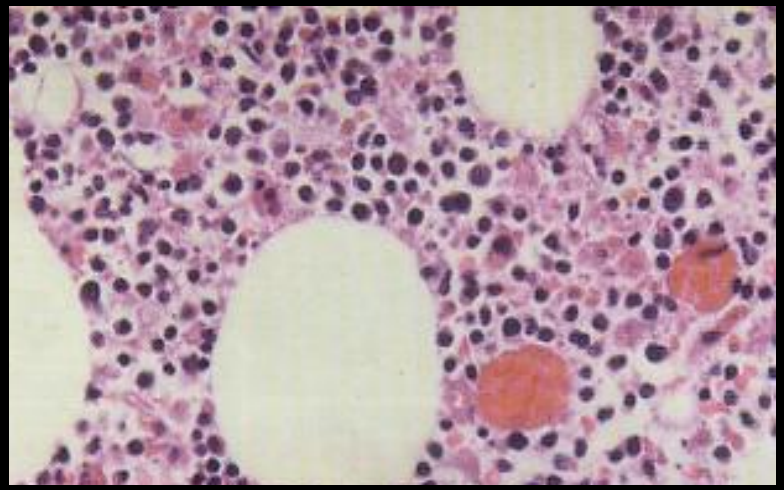
- Circulating leukemic cells are slightly larger than normal large granular lymphocytes
- Some may contain irregular, hyperchromatic nuclei
- Nucleoli can be inconspiscuos or distinct
- Ample amount of pale or slighty basophilic cytoplasm containing fine or coarse azurophilic granules
- The BM show massive, subtle or focal infiltration by the neoplastic cells

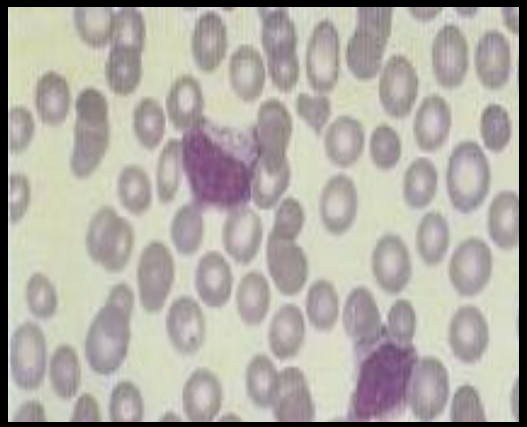
Morphology….

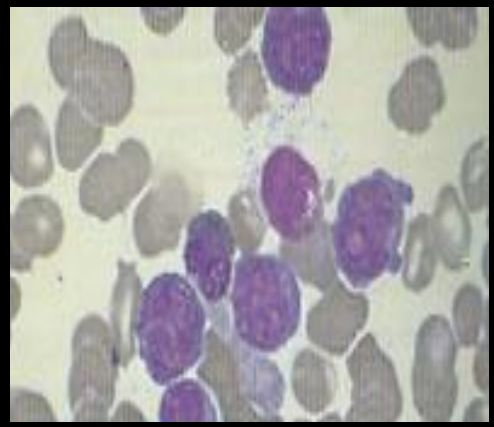
- In the BM the neoplastic cells can be intermingled with reactive histiocytes with hematophagocytosis
- In tissue sections, the leukemic cell show diffuse or patchy destructive infiltrates
- They often appear monotonous, with round or irregular nuclei, condensed chromatin and small nucleoli
- Frequently admixed apoptotic bodies, necrosis is common
- There may be or not angioinvasion

BM

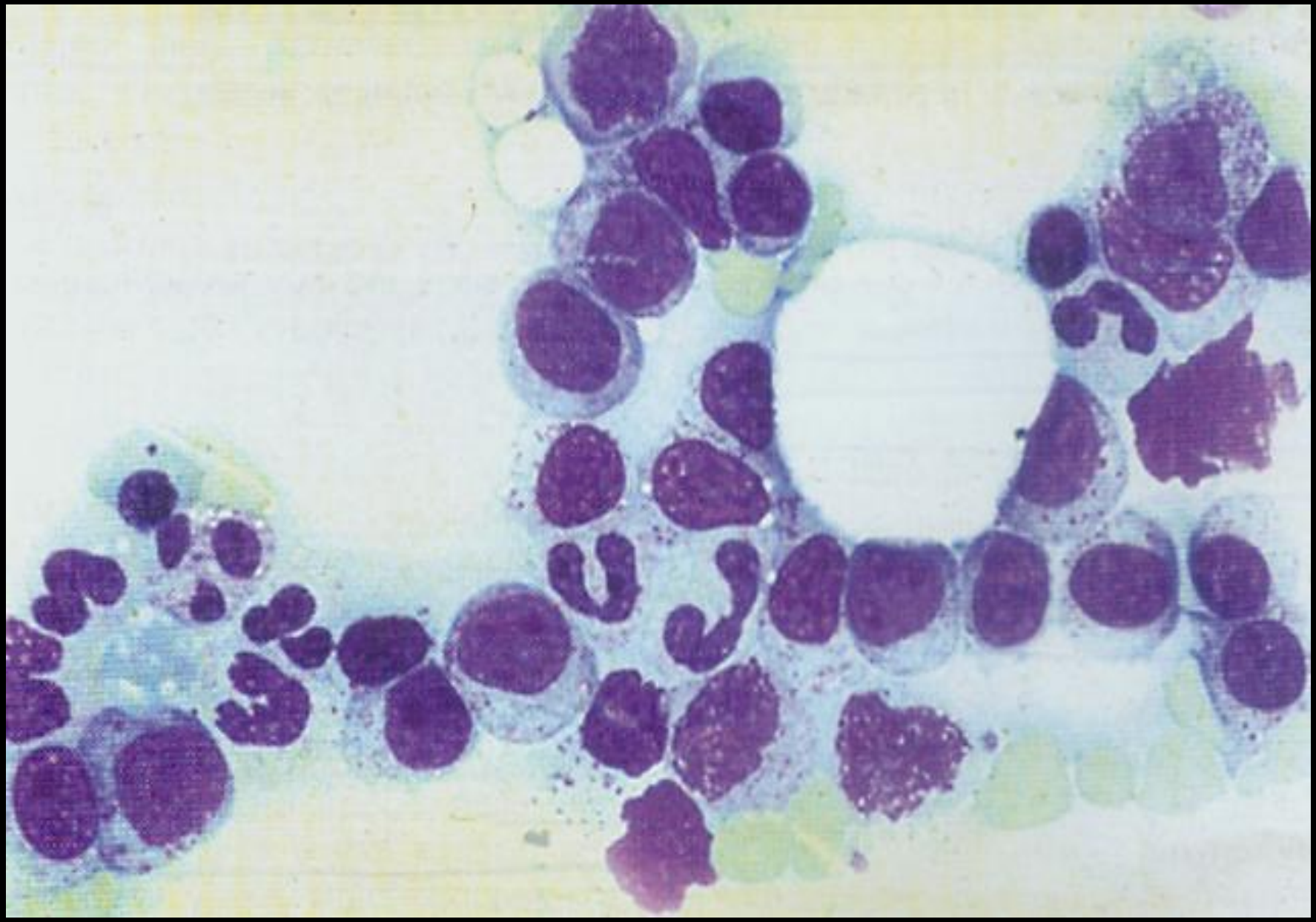








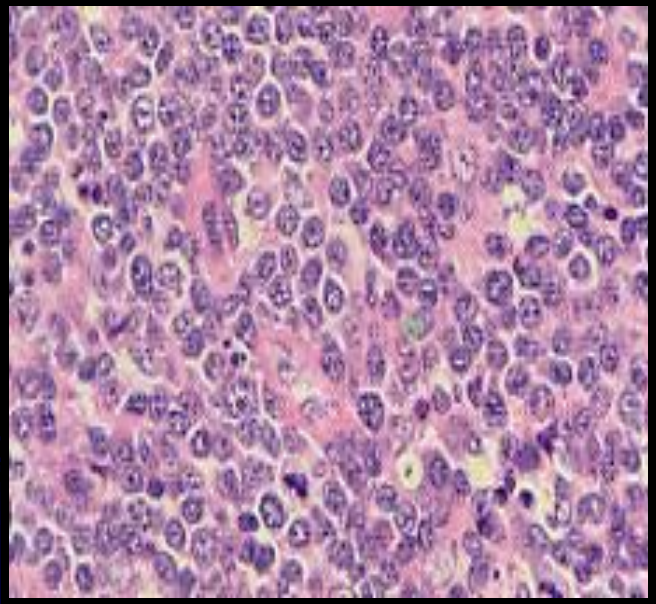
PB



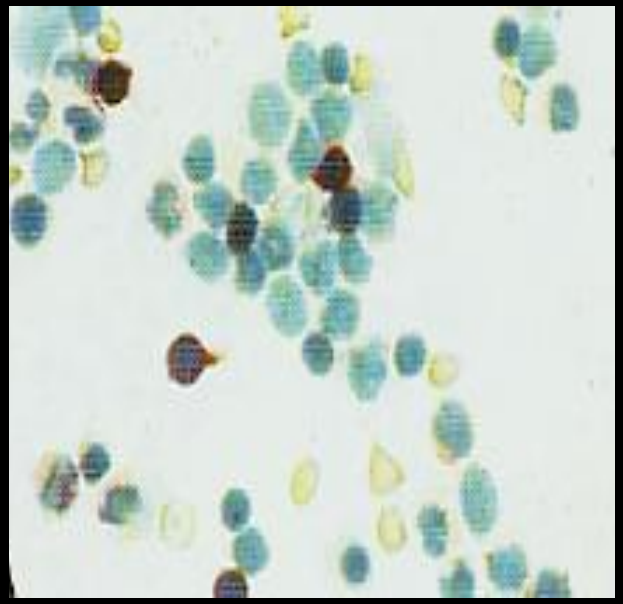
BM aspirate

Immunophenotype

- CD2+, surface CD3-, CD3ε+, CD56+ and positive for cytotoxic molecules
- CD11b and CD16 may be expressed while CD57 is usually negative



Lymph node



CD3 (only stains normal T cells)

CD56

Genetics

- TCR genes are germline configuration
- Clonality has to be established by cytogenetics studies and pattern of X chromosome inactivation in female pts
- The great majority of pts harbour EBV in a clonal episomal form
- A variety of clonal cytogenetic abnormalities have been reported, such as del(6)(q21q25)

Postulated Cell of Origin

- NK cells

Prognosis and Predictive Factors

- Most cases pursue an aggressive course
- Many pts die within days to weeks of initial presentation

Distinction from Indolent NK-cell Lymphoproliferative Disorder

- Not all large granular lymphocyte proliferations with an NK-cell phenotype are aggressive
- There is a form of indolent NK-cell LPD, known as chronic NK-cell lymphocytosis or NK-cell large granular lymphocyte lymphocytosis

Distinction

- Only exceptional cases transform to an aggressive phase
- Indolent NK-cell LPD occur mostly in adults
- Most pts are asymptomatic
- Persistent increase in circulating large granular lymphocytes

Distinction

- There is no fever, hepatosplenomegaly or lymphadenopathy
- There is no association with red cell aplasia, neutropenia or RA
- The immunophenotype of the large granular lymphocytes is: CD2+, surface CD3-, CD56+, CD16+, CD57+
- EBV is negative and TCR genes do not show rearrangements
- Currently it is not clear whether the condition is reactive or neoplastic