# Merged Slides for Lectures 8+9+10

## Our outline:

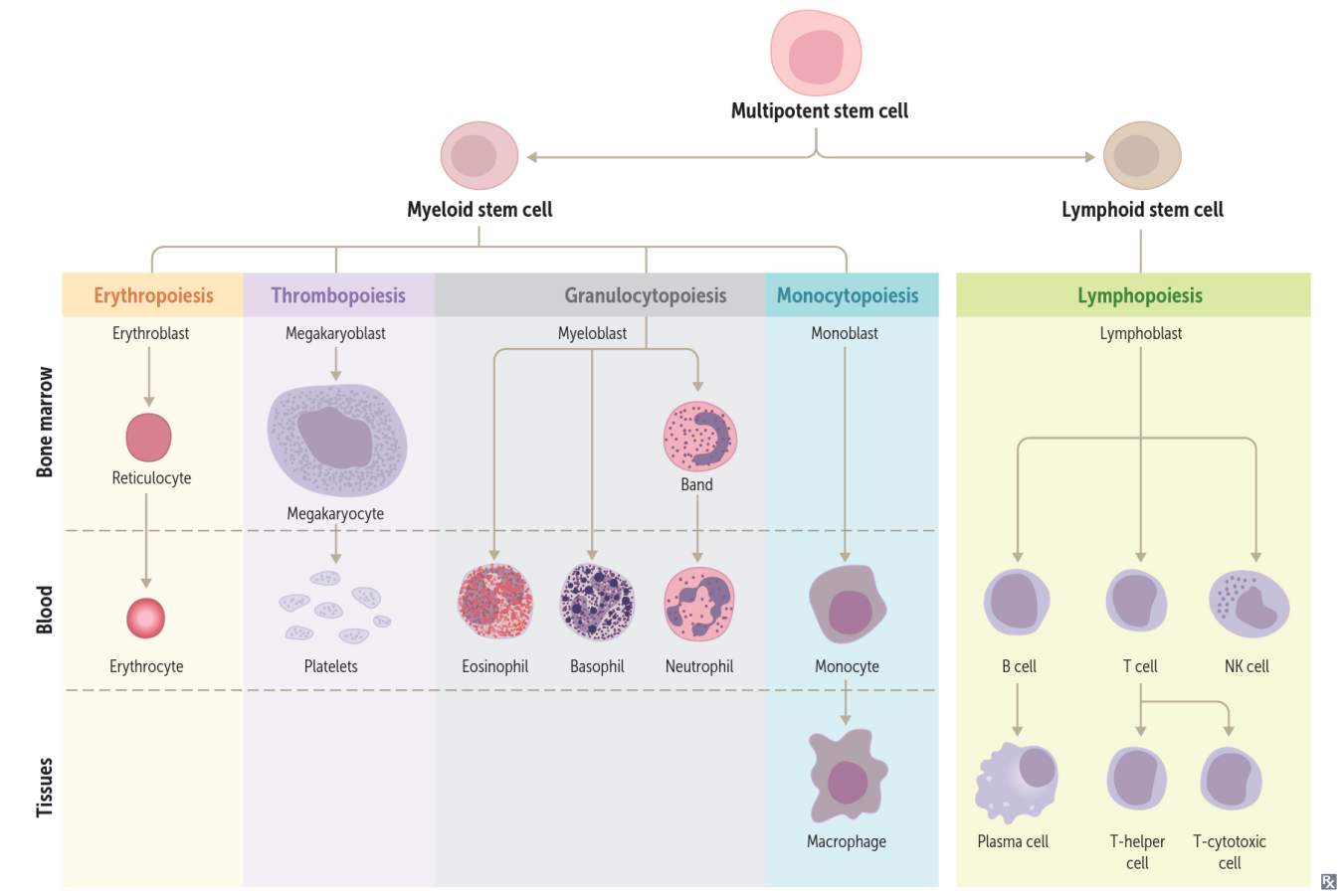
1- Lymphomas

2- Multiple Myeloma

3- Myeloid Neoplasms

4- Acute Lymphoblastic Leukemia

5- Chronic Lymphocytic Leukemia



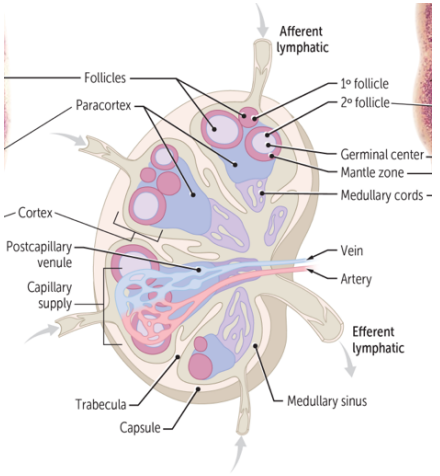
# BURKITT LYMPHOMA

- Most common NHL in children
- Three types:

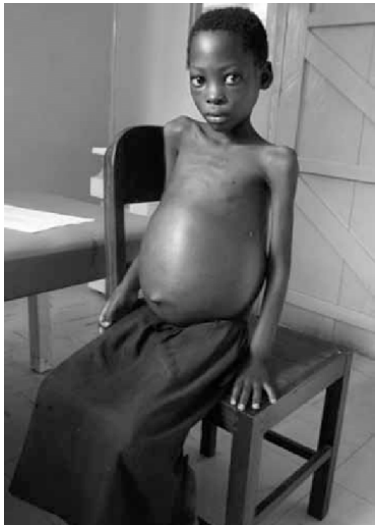
1) Endemic in parts of Africa (100% EBV +)
2) Sporadic in the rest of the world (20% EBV +), latent infection
3) Immunodeficiency associated BL

- Extranodal disease: jaw (endemic), terminal ileum, retroperitoneum, ovary, CNS (sporadic), sometimes leukemic

# PATHOGENESIS



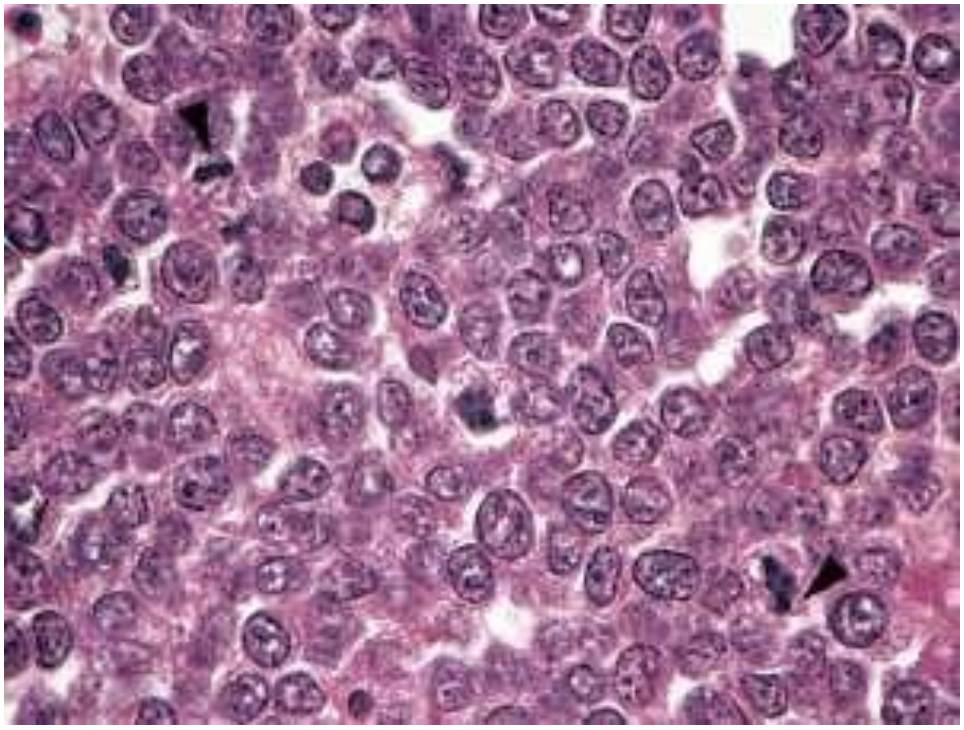

- t(8;14) MYC→IgH
- Overexpression of MYC transcription factor, potent regulator of Warburg metabolism (aerobic glycolysis)
- Neoplastic lymphocytes are B-cells of germinal center origin (CD20, Bcl6)
- Aggressive, but responsive to chemotherapy



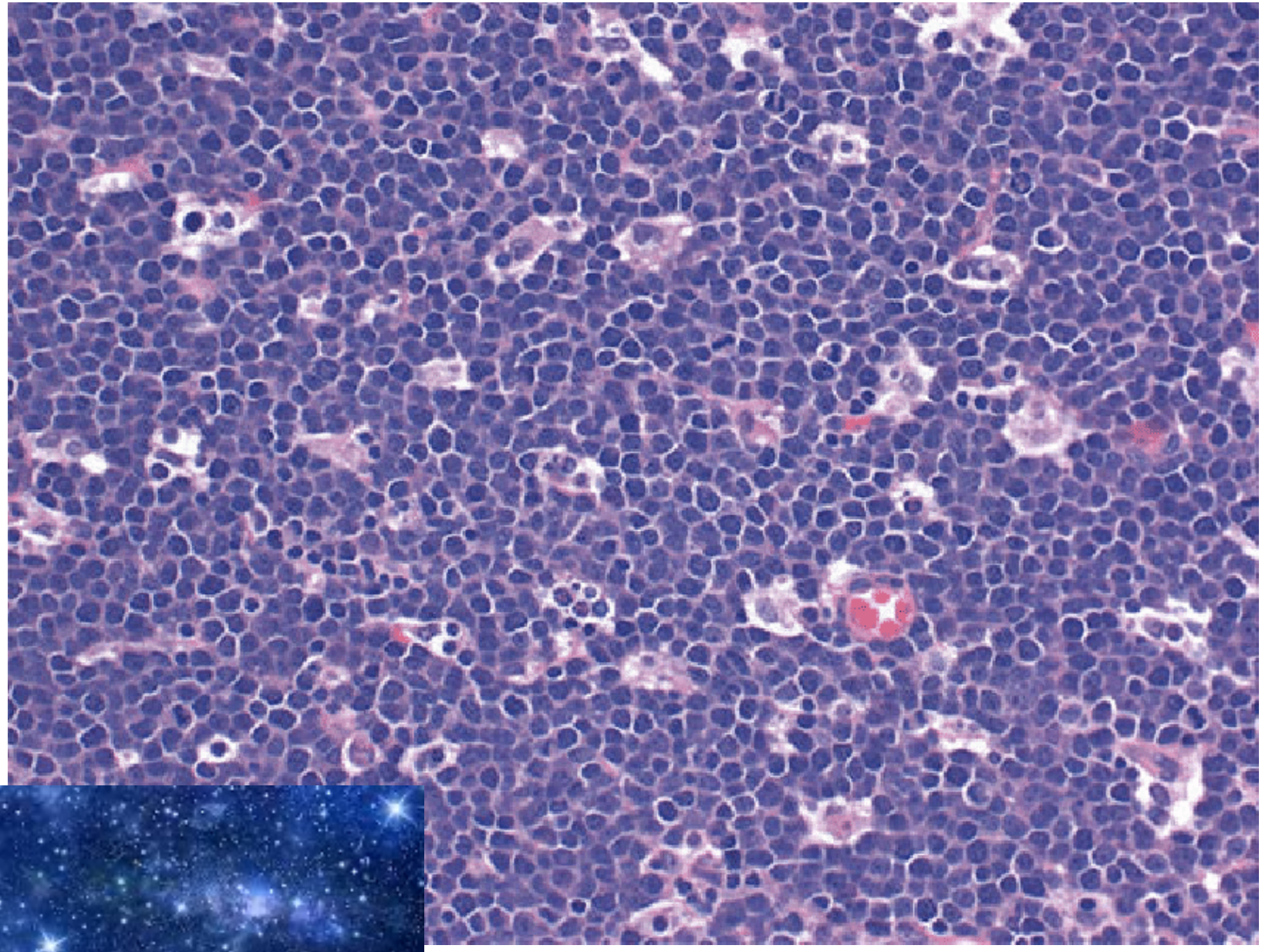
# MORPHOLOGY

- Intermediate size cells
- Monomorphic
- Round or oval, multiple small nucleoli
- Lipid vacuoles in cytoplasm
- Very high mitosis, tangible body macrophages engulfing nuclear debris

1. Small B cells - follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma (i.e., CLL cells that involve tissue)
2. Intermediate-sized B cells - Burkitt lymphoma
3. Large B cells - diffuse large B-cell lymphoma



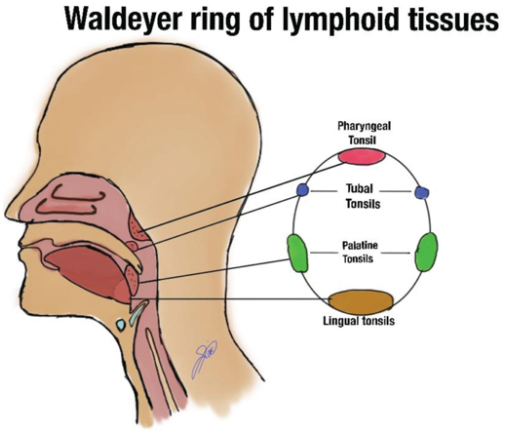
- Neoplastic lymphocytes are monotonous and uniform, multiple small nucleoli, brisk mitosis



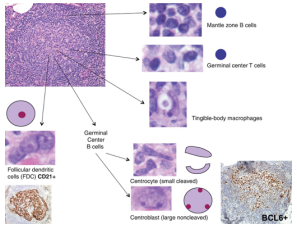
# EXRANODAL MARGINAL ZONE LYMPHOMA

- Indolent B-cell lymphoma
- Second most common lymphoma in extranodal sites in adults
- Arises in the setting of chronic inflammation
- Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjogren syndrome)
- Can complicate Helicobacter pylori-chronic gastritis
- Infiltrate the epithelium and causes destruction

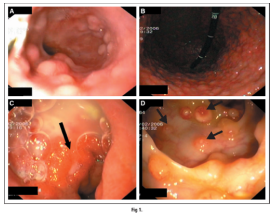
# MANTLE CELL LYMPHOMA




- Arises from naïve B-cells in mantle zone
- Most commonly in older men
- t(11;14) that fuses cyclin D1 gene to IgH locus
- Overexpression of cyclinD1, promote progression of cell cycle
- Affects LNs, Waldeyer ring
- Commonly involve BM, blood in 20%, sometimes in GIT, appears as submucosal nodules (lymphomatoid polyposis)
- Morphology: small centrocytes, but in diffuse pattern



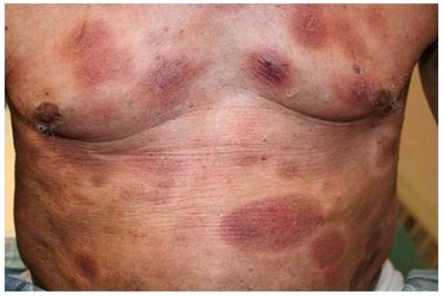

a distinctive and particularly rare clinical type of malignant gastrointestinal lymphoma, which is classified as B-cell centrocytic non-Hodgkin's lymphoma. this rare entity has been recently reclassified as mantle cell lymphoma.



# PERIPHERAL T-CELL LYMPHOMA

- Most common mature T-cell lymphoma
- Aggressive, poor prognosis
- Neoplastic cells secrete inflammatory cytokines, causing severe inflammation
- Positive for CD2, CD3, CD5, CD7

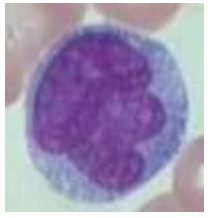
# MYCOSIS FUNGOIDES AND SEZARY SYNDROME



- Neoplastic CD4+ T-cells, that home to skin
- Patients present with erythema, progressive to plaque then tumor
- Neoplastic lymphocytes have irregular nuclear membrane (cerebriform), affecting epidermis and dermis.
- With disease progression, lymphoma disseminates to LNs and viscera

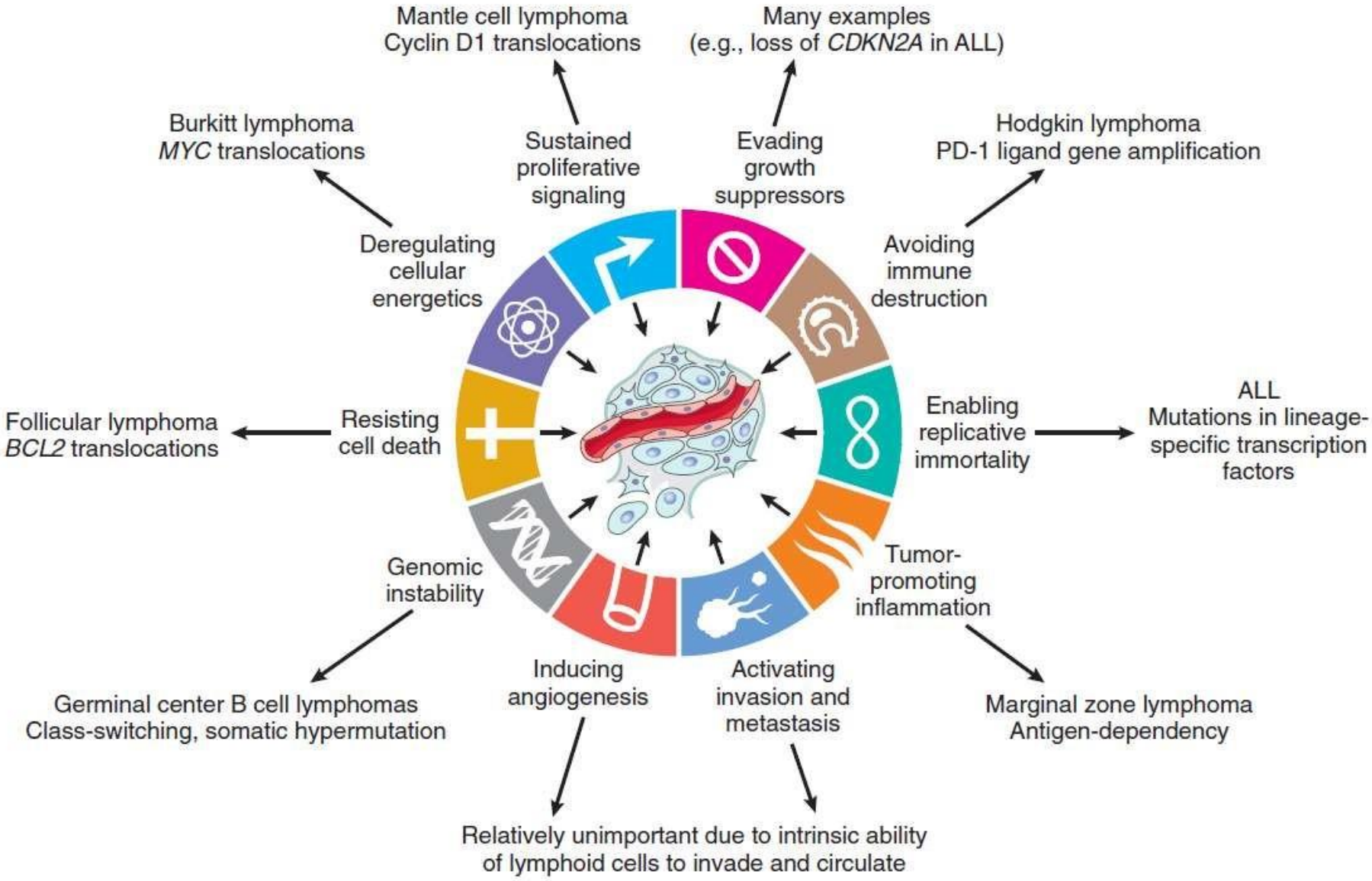
T-cell leukemia

- Sezary syndrome: a variant of MF, patients present initially with widespread erythema and blood leukemia of neoplastic cells (Sezary cells)



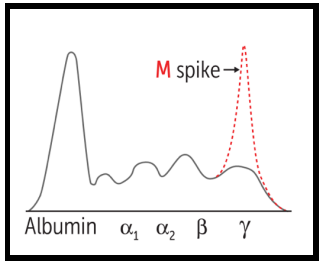
# ADULT T-CELL LEUKEMIA/LYMPHOMA

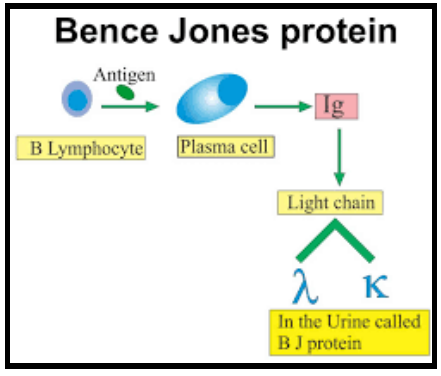
- Neoplastic CD4+ T-lymphocyte
- Caused by a retrovirus; human T-cell leukemia virus 1 (HTLV-1)
- Endemic in Japan, Caribbean basin, West Africa and some parts of South America
- Sporadic everywhere
- Virus is transmitted through body fluids (blood, breastfeeding, sexual intercourse)
- 5% of carrier develop neoplasm, after a latent period of 40-60 years
- Tax protein is essential for viral mRNA transcription, also interacts with PI3 kinase and cyclin D, represses expression of CDK inhibitors, and activates NF-kB, all promote cell survival. Tax also causes genomic instability, inhibiting DNA-repair
- Patients present with skin lesions, lymphadenopathy, lymphocytosis, hepatosplenomegaly and hypercalcemia
- Neoplastic cells express CD25 (IL-2 receptor)
- Poor prognosis


Mantle cell lymphoma
Cyclin D1 translocations
Many examples
(e.g., loss of *CDKN2A* in ALL)
Burkitt lymphoma
*MYC* translocations
Sustained proliferative signaling
Evading growth suppressors
Hodgkin lymphoma
PD-1 ligand gene amplification
Deregulating cellular energetics
Avoiding immune destruction
Follicular lymphoma
*BCL2* translocations
Resisting cell death
Enabling replicative immortality
ALL
Mutations in lineage-specific transcription factors
Genomic instability
Tumor-promoting inflammation
Germinal center B cell lymphomas
Class-switching, somatic hypermutation
Inducing angiogenesis
Activating invasion and metastasis
Marginal zone lymphoma
Antigen-dependency
Relatively unimportant due to intrinsic ability of lymphoid cells to invade and circulate

# PLASMA CELL MYELOMA

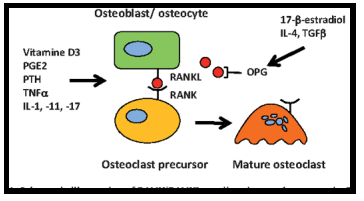
- AKA multiple myeloma
- Common neoplasm
- Commonly in elderly, more common in men, African origin
- Malignant plasma cells secrete monoclonal protein (M protein), most commonly IgG (60%), then IgA (20-25%), followed by other types.
- Sometimes only light chain (kappa or lambda), can be detected in urine (Bence Jones proteins)



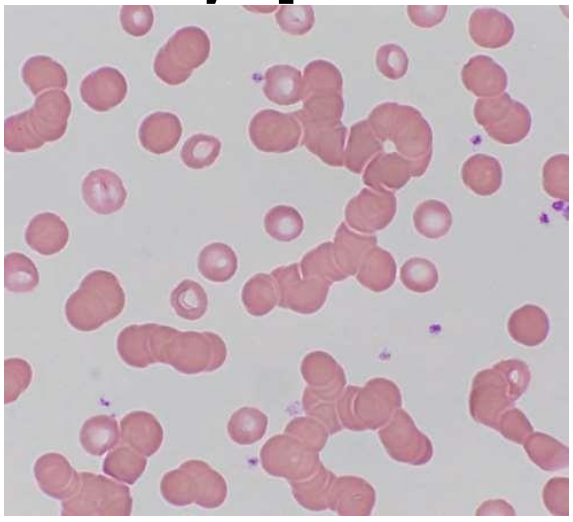
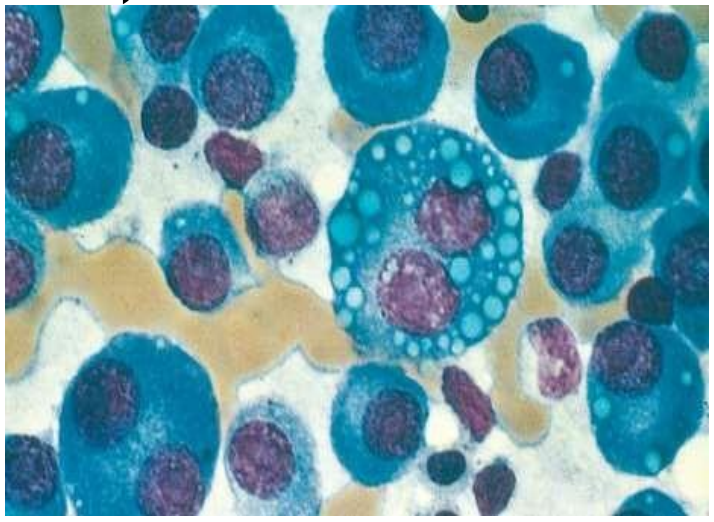
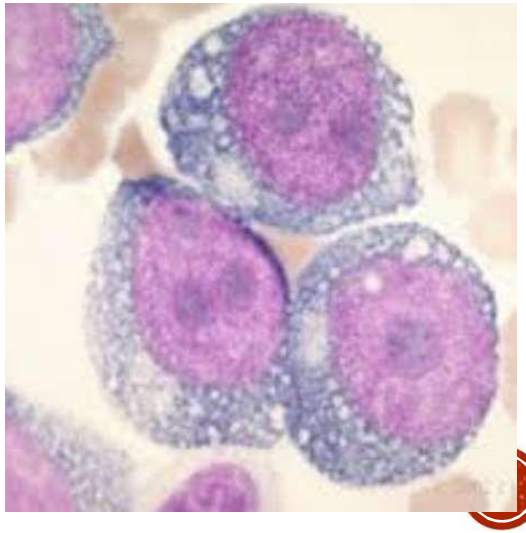
# PATHOGENESIS

- t(11;14) IgH-cyclinD1 and cyclinD3
- MYC gene mutation occurs late in disease
- IL-6 is important is plasma cell survival, secreted from BM macrophages and fibroblasts
- Malignant plasma cells activate expression of receptor activator of NF-kB ligand (RANKL), that activates osteoclasts, causing bone resorption. Other products inhibit osteoblast function (hypercalcemia and pathologic fracture)
- Suppression of normal B-cell function
- Directly inhibits erythropoiesis (early onset anemia)
- Renal failure: obstruction to distal collecting tubules by proteinaceous cast (Bence Jones protein, immunoglobulin, albumin). Hypercalcemia produces kidney stones, causing further obstruction and renal infection



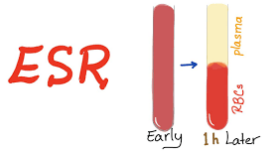
# MORPHOLOGY

- Peripheral blood: RBCs show rouleaux formation
- BM: increased number of plasma cells (>10% of bone marrow cells) with clock-face chromatin and intracytoplasmic inclusions containing IgG.
- Morphologically might resemble normal plasma cells, or become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles)

# CLINICAL AND LABORATORY FINDINGS

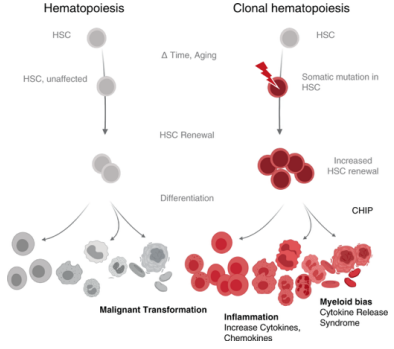
- Very high ESR




- CRAB (hypercalcemia, renal failure, anemia, bone fracture)
- Amyloidosis: occurs in few patients, secondary to deposition of light chain (AL-amyloid)
- In advanced disease: pancytopenia, plasma cell leukemia, visceral damage
- Slowly growing, not curable with conventional chemotherapy
- Lenalidomide: inhibits oncogenic proteins
- Proteasome inhibitors: inhibit degradation of misfolded proteins. When accumulate, cause apoptosis in plasma cells

# MYELOID NEOPLASMS

- Arises from hematopoietic progenitor stem cells
- Neoplastic cells proliferate and efface normal hematopoietic cells
- Divided into:
- Acute myeloid leukemia: impaired maturation, increased proliferation (myeloblast)
- Myeloproliferative neoplasms: normal maturation, increased proliferation
- Myelodysplastic syndrome: abnormal maturation, normal proliferation
- MPN and MDS can transform to AML
- BM is hypercellular in all myeloid neoplasms
- Clonal hematopoiesis of indeterminant prognosis (CHIP): represents a precursor for AML and MDS, patient has normal cell count despite the presence of a clone with a mutation



# MYELODYSPLATIC SYNDROME

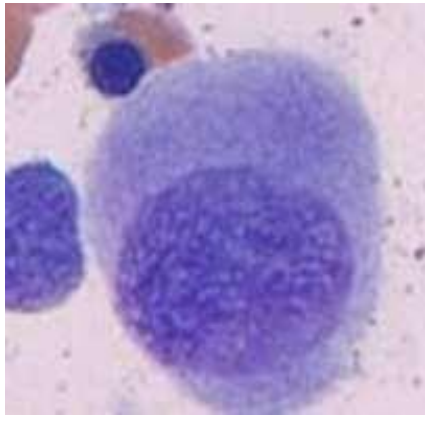
- Main feature is defective maturation, ineffective hematopoiesis, high risk for transformation to AML
- BM is replaced by a clonal progeny of transformed stem cell that has an capacity to differentiate into 3 cell lines but with abnormal morphology and function
- Hallmark of MDS: hypercellular BM, peripheral cytopenia and morphologic dysplasia
- Tendency for accumulating more mutations and transform to AML
- Most cases are idiopathic, rarely follows chemo or radiotherapy (therapy related)
- Most patients are old

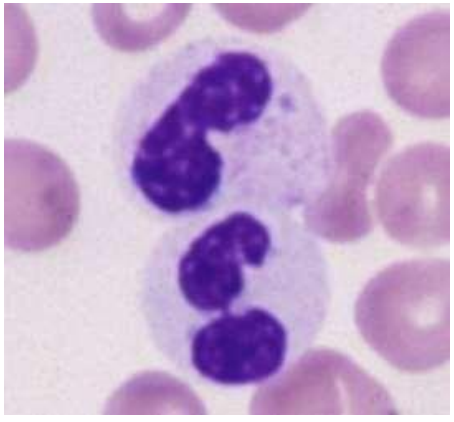
# PATHOGENESIS

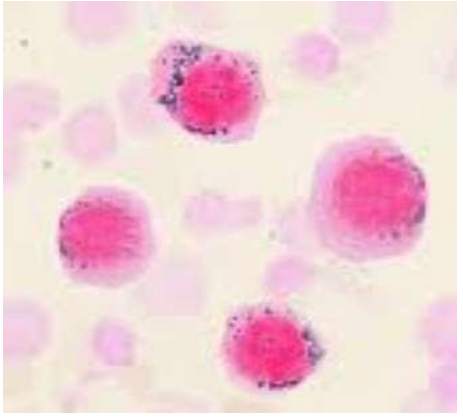
- Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8
- Mutations in epigenetic factors that regulate DNA methylation and histone modifications
- RNA splicing factors: abnormal RNA processing → ring sideroblasts
- Transcription factors
- 10% have P53 mutation

# MORPHOLOGY

- Erythroid: macrocytic anemia, megaloblastoid nuclei, ring sideroblasts (iron accumulation inside mitochondria)
- Myeloid: decreased granulation, hyposegmented nuclei of neutrophils
- Megkaryocytes: small, hypolobated nuclei
- Myeloblasts: can be increased, but <20% of nucleated cells







# SYMPTOMS

- Refractory anemia, thrombocytopenia, neutropenia
- Survival 9-29 months

# ACUTE MYELOID LEUKEMIA

Unregulated growth and differentiation of WBCs in bone marrow  marrow failure  anemia ( RBCs), infections ( mature WBCs), and hemorrhage ( platelets).

- Occur at all age groups, but more common in elderly
- Heterogenous, diagnosis is made by morphologic, immunophenotypic and karyotype studies
- Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies
- Symptoms are accelerated, become significant within few weeks
- Symptoms are related to anemia, thrombocytopenia and neutropenia
- Involvement of LN, spleen and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia)

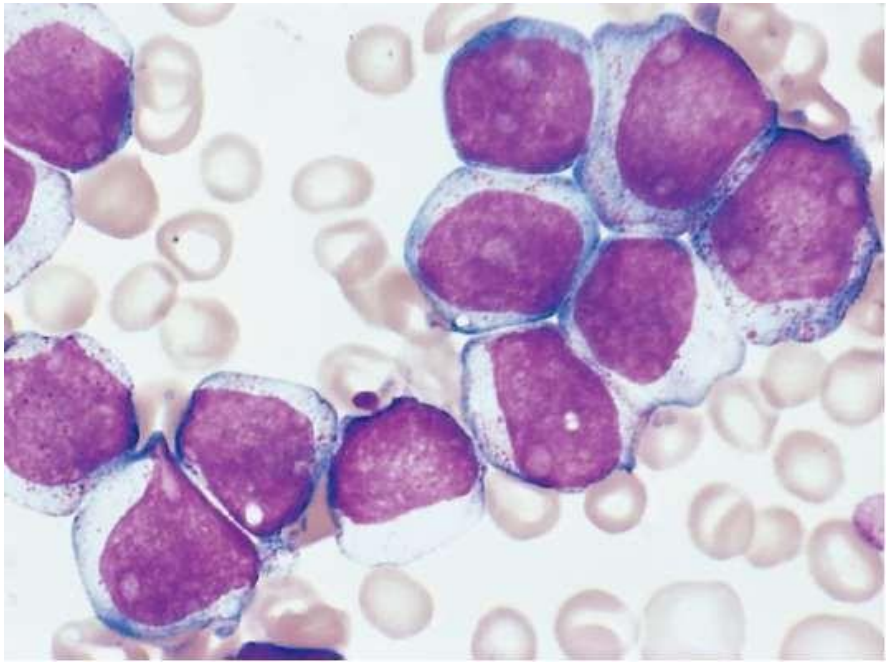
# PATHOGENESIS

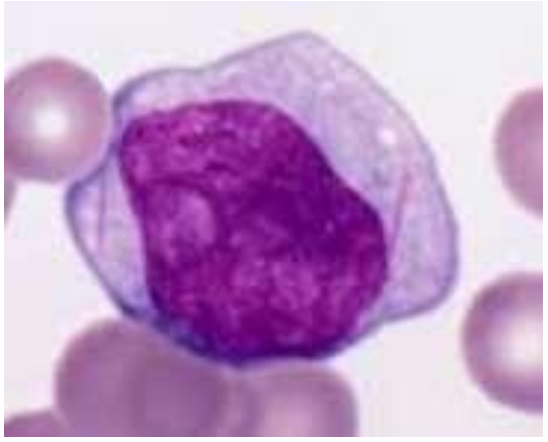
- Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts
- Additional mutations in tyrosine kinase pathways (RAS)
- Epigenetic mutation is common (20%); mutation is isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation

# WHO-CLASSIFICATION

- Therapy related AML: occurs after treatment with chemo or radiotherapy
- AML with recurrent cytogenetic mutation
- AML with myelodysplasia: occurs de novo or complicates MDS
- AML-Not otherwise specified

- Diagnosis of AML: 20% blasts in peripheral blood or bone marrow (of nucleated cells)





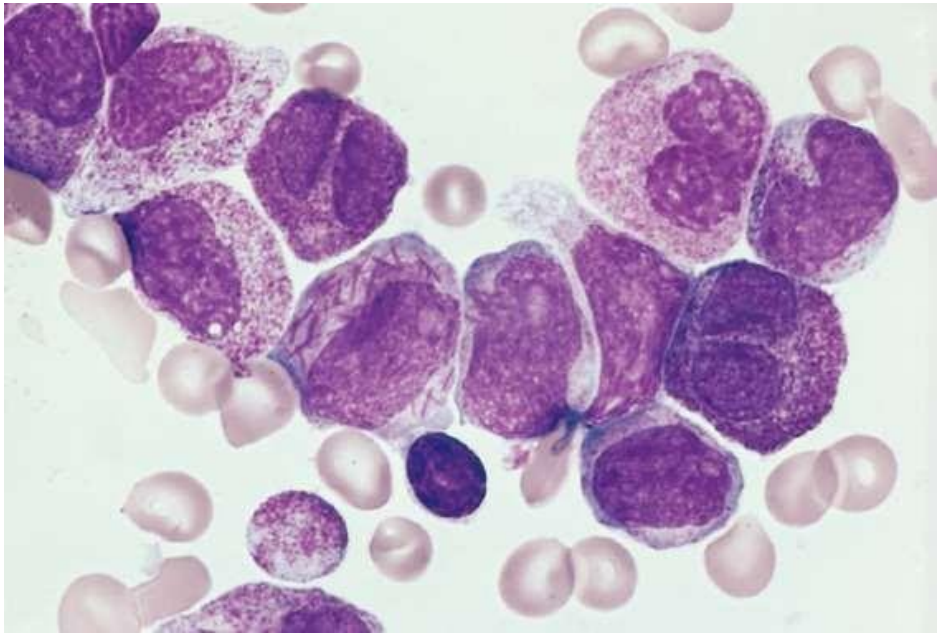
- Morphology: large cells, high N/C ration, fine granules in cytoplasm, fine chromatin, prominent nucleoli
- Auer rods: small pink rods present in cytoplasm, represent peroxidase enzyme
- Myeloblasts express CD34, myeloperoxidase (MPO), CD13, CD33
- Sometimes: monoblast, erythroblast, megakaryoblast

# OUTCOME

- Generally poor, <30% responds to chemotherapy
- Worse than ALL
- P53 mutation: worse outcome
- IDH inhibitors are new promising drugs
-

# ACUTE PROMYELOCYTIC LEUKEMIA

- Also called AML-M3
- Maturation is arrested at promyelocyte stage
- Leukemic cells appear similar to promyelocytes (heavy cytoplasmic granules, numerous Auer rods, negative for CD34)
- Carry recurrent mutation: t(15;17) fusion between PML gene (chrom 15) with alpha retinoic acid receptor (RARA) on chrom 17. Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid.
- All trans-retinoic acid (ATRA), a vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein)
- Malignant promyelocyte secrete tissue factor, causing DIC

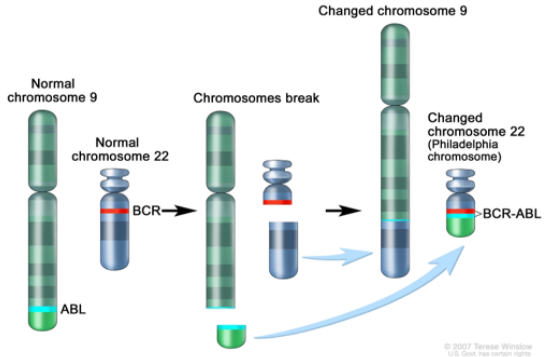


- APL: malignant promyelocytes show numerous cytoplasmic granules and Auer rods. The nuclei are commonly cleaved.

# MYELOPROLIFERATIVE NEOPLASMS

- Maturation is normal, but proliferation is high
- Permanently active tyrosine kinase pathway, independent from growth factors
- BM is hypercellular, peripheral blood shows cytosis
- Neoplastic stem cells in MPN often seeds to spleen, liver and occasionally LNs, causing extramedullary hematopoiesis and thus hepatosplenomegaly
- Tendency to transform to AML

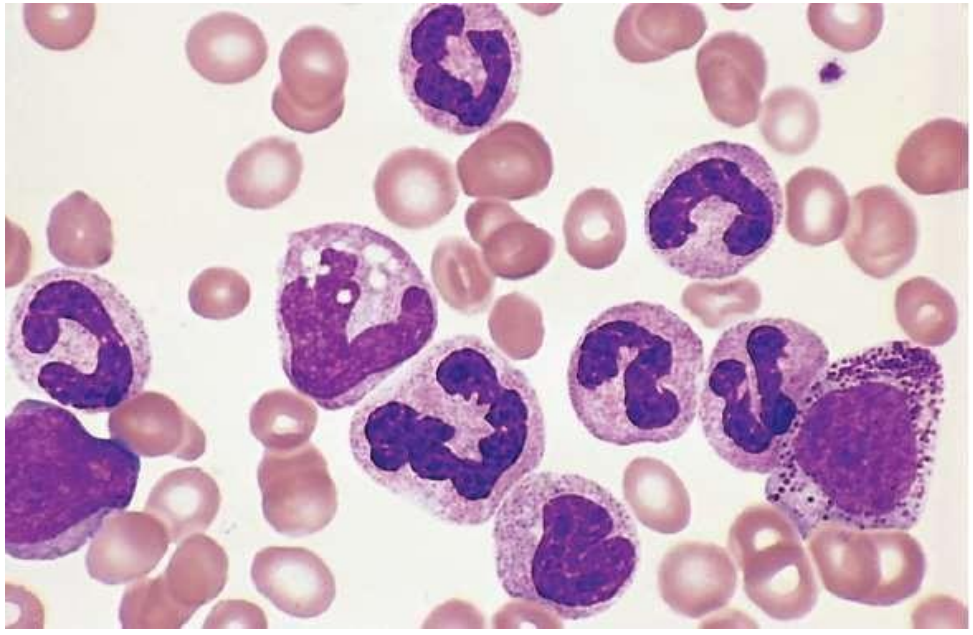
# CHRONIC MYELOID LEUKEMIA




- Most common MPN
- Harbor t(9;22) □ Philadelphia chromosome, results in fusion of Bcr/Abl genes and production of a tyrosine kinase that results in prolonged cell survival
- Mutation is present in all BM cells (myeloid, erythroid and megs)
- Affects adults 25-60 years
- Symptoms: non-specific: fatigue, heavy abdomen, weight loss
- Imatinib: tyrosine kinase inhibitor, specific for bcr/abl mutation
- Accelerated phase: worsening of symptoms, higher WBC count, thrombocytopenia, resistance to imatinib
- Blast crisis: transformation to acute leukemia (AML>ALL)

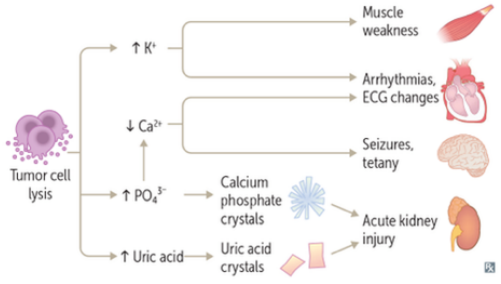
# MORPHOLOGY OF CML

- Leukocytosis, can be >100K
- Shift to left
- Basophilia, eosinophilia
- Thrombocytosis
- Anemia
- BM: increased nyeloid and megs
- Spleen: EMH
- Blasts: low
- Leukemoid reaction: high WBC and shift to left, occurs in severe inflammation
  - No basophilia or eosinophilia



# POLYCYTHEMIA VERA

- Mutation in tyrosine kinase JAK2, normally acts in the signaling pathway of erythropoietin receptor and other growth factor receptors
- Hematopoietic cells become less dependent on growth factors
- Excessive proliferation of erythroid, megs and myeloid (panmyelosis)
- Erythrocytosis is most prominent, results in polycythemia (low erythropoietin level)
- Insidious onset of symptoms, middle age, plethora, sometimes cyanosis, headache, dizziness, pruritis, peptic ulcer
- Thrombosis and tissue infarction, bleeding is also common (GIT), gout
- Spent phase: occurs after an interval of 10 years of symptoms, BM become fibrotic, hematopoiesis shifts to spleen
- Blast crisis: transformation to AML (rare)
- Treatment: phlebotomy, JAK2 inhibitor



# Laboratory findings

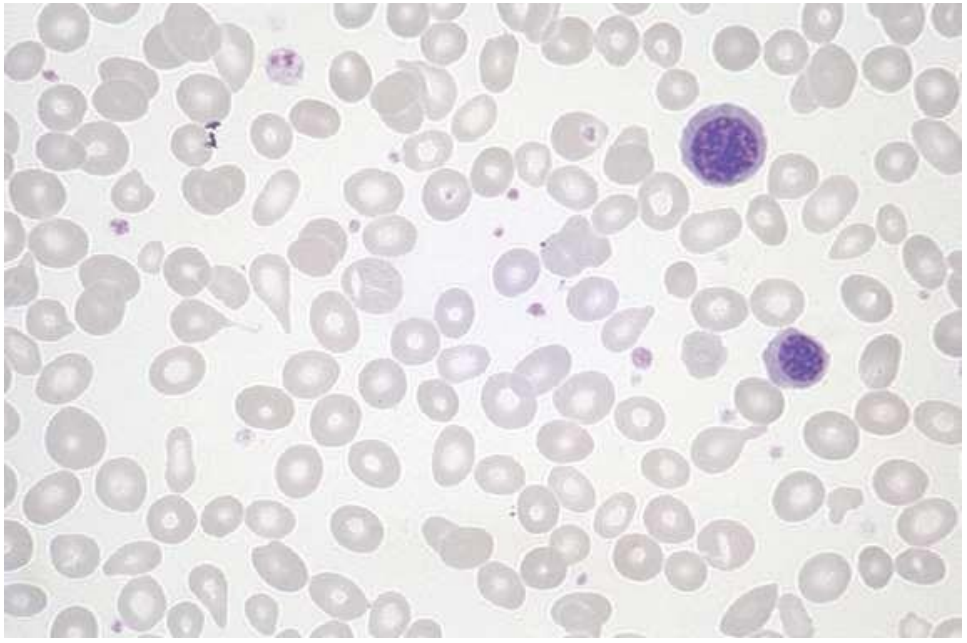
- High RBC count
- Hematocrit 60% of more
- Leukocytosis is common
- Basophilia
- Thrombocytosis is common

# PRIMARY MYELOFIBROSIS

- Over BM fibrosis, reducing capacity for hematopoiesis, leads eventually to cytopenia and massive EMH
- JAK-STAT signaling pathway is active in all cases
- 50% have mutation in JAK2, 5% in MPL gene (thrombopoietin receptor)
- Neoplastic megakaryocytes secrete TGF-B, which activates fibroblasts in BM to deposit reticulin and collagen fibers, also causes angiogenesis
- RBC production is impaired, RBCs appear as tear-drop, patients have anemia

# MORPHOLOGY

- Peripheral blood: tear-drop cells, nucleated RBCs, shift to left (leucoerythroblastic anemia)
- WBC: can be normal of increased
- Plt: high, then low
- BM: early: hypercellular and focal fibrosis, late: hypocellular and extensive fibrosis. Megakaryocytes are increased and form clusters



# CLINICAL FEATURES

- Non-specific symptoms, weight loss, anemia, massive splenomegaly, gout, bleeding, infection
- Worse outcome than CML and P Vera. 4-5 years survival
- Frequent transformation to AML (5-20%)
- JAK2 inhibitor: decreases splenomegaly and symptoms

# ESSENTIAL THROMBOCYTHEMIA

- Predominantly thrombocytosis (occasional leukocytosis)
- JAK2 mutation is sometimes positive, but NO bone marrow fibrosis
- Splenomegaly is positive in 50%
- Good outcome

# LANGERHANS CELL HISTIOCYTOSIS

- Neoplasm of dendritic cells
- Langerhans cells express CD1a and Langerin
- Langerin is a transmembrane protein, attached to Birbeck granules (tennis ricket shape under electron microscope)
- Proliferating Langerhans cells appear large and vacuolated, similar to macrophages
- Pathogenesis: acquired mutation in serin/threonine kinase BRAF, leads to hyperactivity of this kinase

# MULTISYSTEMIC LCH

- Occurs mostly in children less than 2 years
- Multiple cutaneous lesion, composed of LCs
- Hepatosplenomegaly and lymphadenopathy
- Pulmonary lesions
- Osteolytic lesions
- Extensive bone marrow infiltration leads to pancytopenia
- Treated with chemotherapy

# UNISYSTEM LCH

- AKA eosinophilic granuloma
- Affects a single organ, most commonly bone, then skin, lung, stomach
- Can be unifocal or multifocal
- Unifocal is commonly asymptomatic, can cause pain
- Mulfocal unisystem disease presents in children, commonly affects calvaria bone, extends to pituitary gland causing diabetes insipidus, exophthalmous (Hand-Schuller-Christian triad).
- Proliferating LCs are admixed with numerous eosinophils, lymphocytes, plasma cells and neutrophils
- Treatment: unifocal: surgical excision, multifocal: chemotherapy, sometimes spontaneous regression

# PRECURSOR B AND T CELL NEOPLASMS

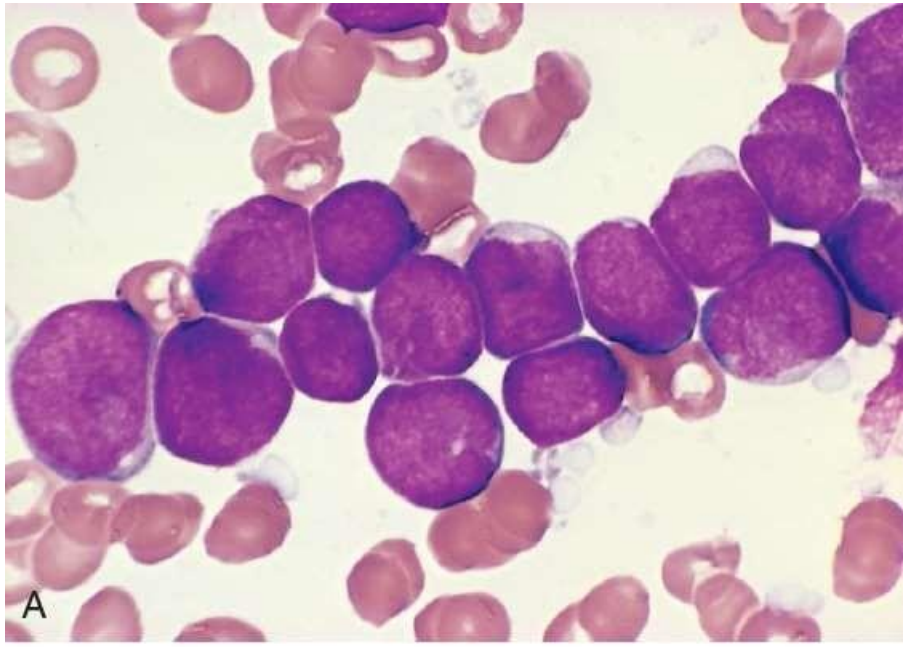
- Lymphoblastic lymphoma when occurs in solid tissue (T>B)
- Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B>T)
- B-ALL is the most common childhood malignancy
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell. Aggressive neoplasms, express CD34 and TDT
- T-ALL is less common, presents in adolescents, involving thymus, more common in boys
- B-ALL tends to disseminate to solid organs (brain, testis, spleen)

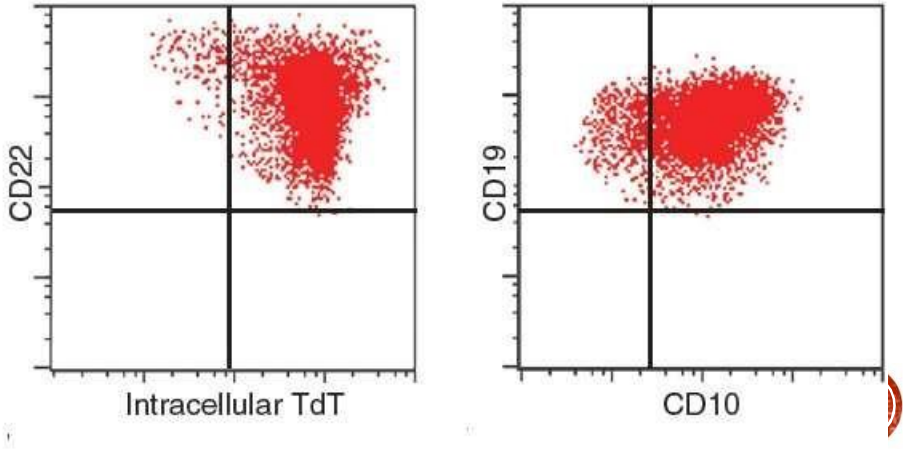
# PATHOGENESIS

- Mutations in transcription factors for genes responsible for maturation of blasts
- In T-LL: 70% have mutations in NOTCH1 gene
- In B-LL, mutation in PAX5 gene
- Mutations in RAS signaling and tyrosine kinase proteins promoting cell survival
- Most childhood B-ALL have hyperdiploidy (>50 chromosomes) and t(12;21), involving ETV6 and TUNX1 genes, creating new transcription factor
- Adult B-ALL exhibits t(9;22) between ABL and BCR genes, similar to chronic myeloid leukemia, creating a new tyrosine kinase protein (imatinib)
- T-ALL shows mutation in PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

# MORPHOLOGY OF ALL

- Blasts are large, high N/C ration
- Chromatin is open (pale)
- Nucleolus sometimes present
- Cytoplasm is not granular



# CLINICAL FEATURES

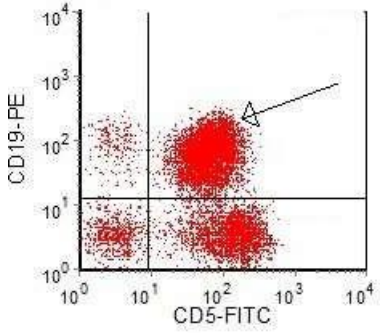
- Anemia, thrombocytopenia
- Damage to solid organs secondary to leukemic infiltration
- Favorable prognostic factors in B-ALL: hyperdiploidy, low WBC count, age between 2-10 years
- Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults, WBC count >100k

# SMALL LYMPHOCYTIC LYMPHOMA/ CHRONIC LYMPHOCYTIC LEUKEMIA

- Low-grade B-cell neoplasm
- Affects elderly
- Can arise in LNs and solid tissue (SLL), or in BM and peripheral blood (CLL)
- Most common leukemia in adults, while SLL represents only 4% of NHL
- Not common in Asia

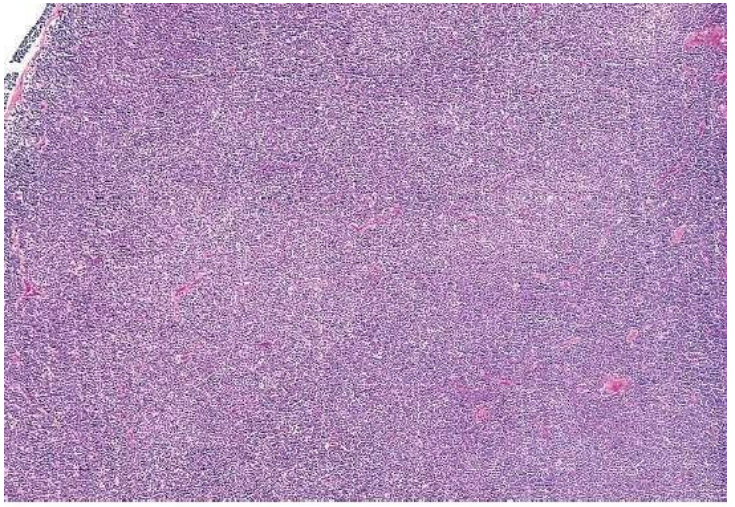
# PATHOGENESIS

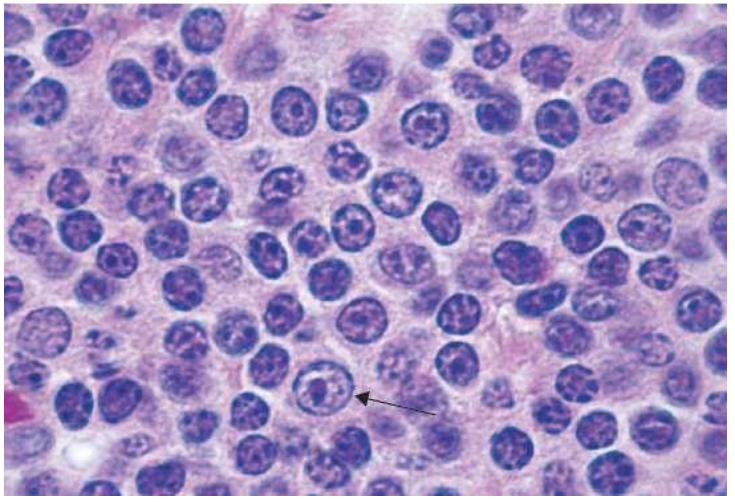
- Increased Bcl2 protein, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators of Bcl2
- A surface immunoglobulin called B-cell receptor (BCR), is autonomously active, activating a intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell survival
- Chromosomal translocation is rare
- Lymphoma cells express CD20, Bcl2 and CD5



# MORPHOLOGY OF SLL

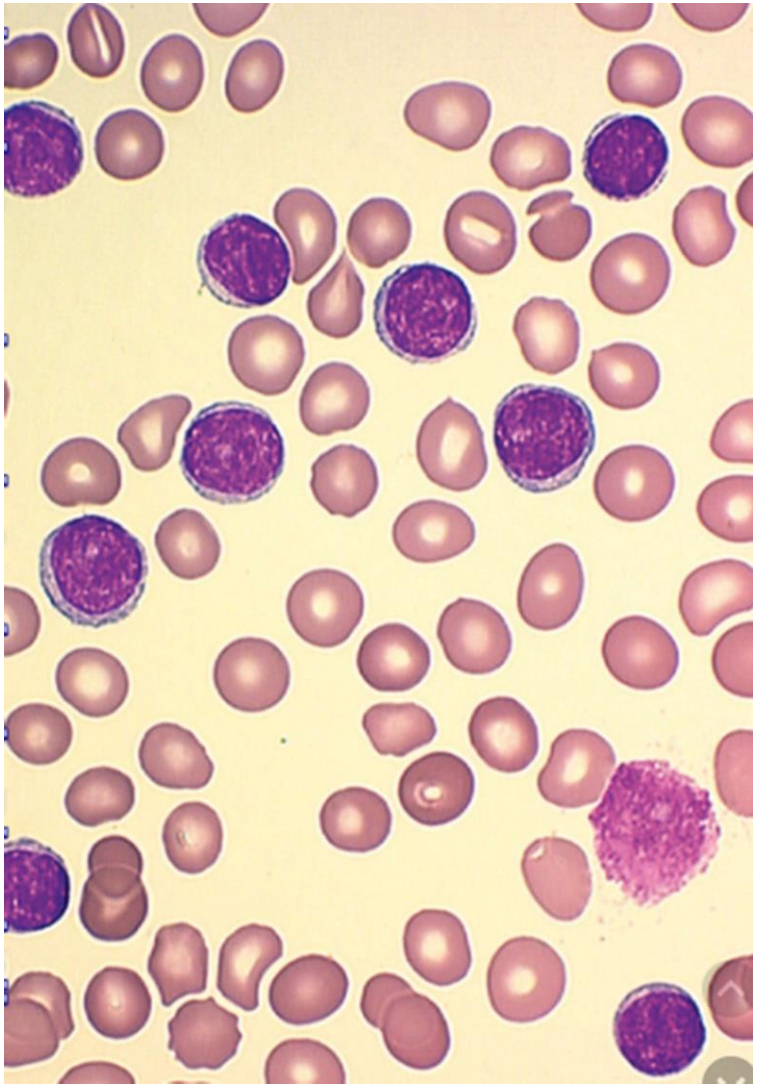
- LN shows effacement of architecture
- Most of neoplastic cells are small in size, round, dark chromatin, along with few large cells with central prominent nucleolus (prolymphocyte)
- Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis





# MORPHOLOGY OF CLL

- Leukemic cells appear similar to lymphocytes
- Occasional prolymphocytes
- Smudge cells



# CLINICAL FEATURES

- Many patients are asymptomatic
- Leukocytosis can reach very high levels (>200,000)
- 50% have generalized lymphadenopathy and hepatosplenomegaly
- Immune dysfunction is common, by suppressing normal B-cells, resulting in hypogammaglobulinemia (50% of patients)
- Anemia: 15% of patients develop auto antibodies against RBCs and platelets (cold type), secreted by normal B-cells
- Thrombocytopenia: similar to ITP
- Variable outcome: many patients have similar survival to general population. In contrast, P53 mutation makes prognosis worse
- Richter transformation: predominance of large cells, patients survive <1 year

# HAIRY CELL LEUKEMIA

- Uncommon low-grade B-cell leukemia
- Affects older patients, more common in men, smokers
- Leukemic cells are few in number, have prominent cytoplasmic projections
- Splenomegaly, pancytopenia (Leukemic cells heavily infiltrate BM and spleen)
- Leukemic cells are biologically active, inhibit hematopoiesis and cause bone marrow fibrosis
- LN involvement is very rare
- Mutation in serine/threonine kinase BRAF gene
- Very sensitive to chemotherapy