PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM–

Dr. Tariq Al-Adaily, MD
Associate Professor
Department of Pathology
The University of Jordan
Email: TNALADILY@ju.edu.jo

School of Medicine

NEOPLASTIC PROLIFERATION OF WBC

- Mostly considered as malignant, fluid tumors
- Differs in biologic behavior, ranging from indolent to very aggressive cancers
- Common cancers
- Current classification system: World Health Organization (WHO) classification system for Hematolymphoid neoplasms
- Classified according to lineage (myeloid vs lymphoid, B vs T, etc…), based on morphology, protein and molecular tests

LYMPHOMA

- Neoplasm of lymphocyte, malignant
- Called leukemia if affects bone marrow or peripheral blood, lymphoma if affects lymph nodes or solid organs (extranodal lymphoma)
- Classified into Hodgkin and non-Hodgkin lymphoma
- Non-Hodgkin lymphoma is classified into B and T-cell lymphoma
- B-cell lymphomas are more common, involve immunoglobulin gene (accidents during class-switch)
- All are malignant, but can be of low-grade (indolent) or high-grade (aggressive)
- Diagnosis is made through morphologic and immunophenotypic (immunohistochemistry or flow cytometry) examination of biopsy
- Sometimes a test for mutations is performed
- Immunodeficiency is a risk factor for lymphoma, and vice versa

COMMONLY TESTES IMMUNOPHENOTYPES

- CD45: common leukocyte antigen
- B-cells express CD19, CD20, CD22
- T-cells express CD2, CD3, CD5, CD7
- Germinal center lymphocytes express CD10 and Bcl6
- Plasma cells express CD138
- T-helper lymphocytes express CD4
- Cytotoxic lymphocytes express CD8
- Blasts express CD34
- Lymphoblasts express TDT (terminal deoxynucleotidyl transferase) and CD10

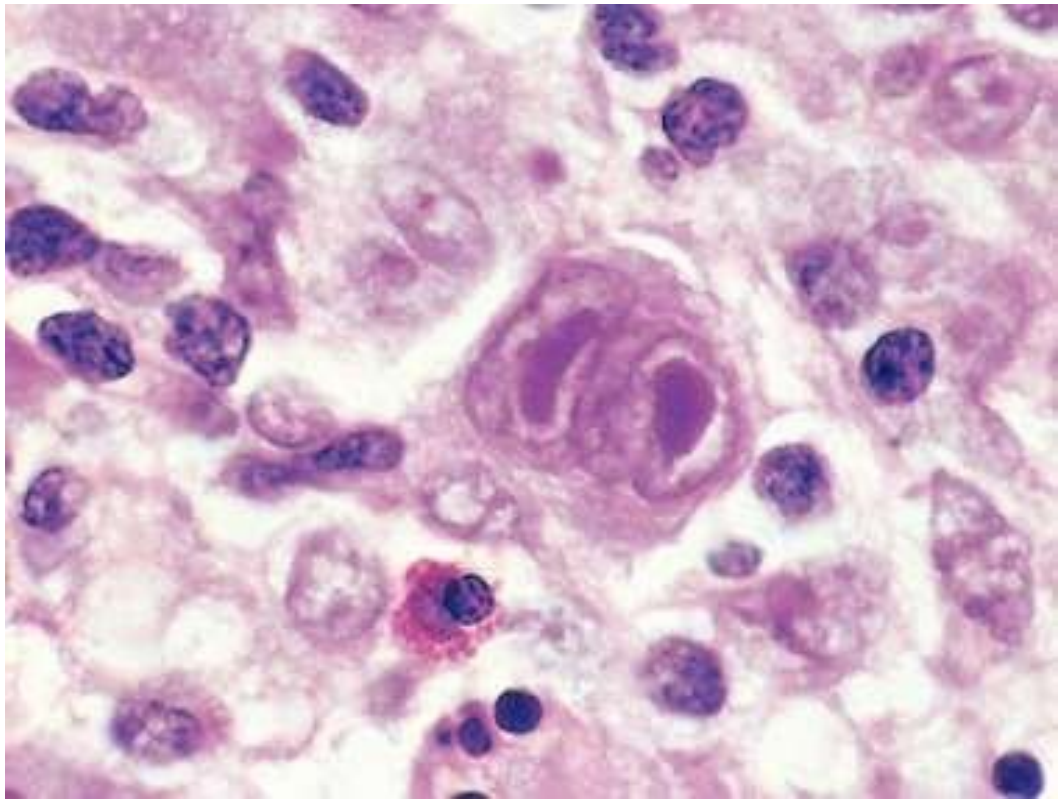
HODGKIN LYMPHOMA

- Constitutes 30-40% of all lymphomas
- Most common type of lymphoma in Jordan, in children and young adults
- The neoplastic cells are giant, different morphology and immunophenotype from normal lymphocytes, forms less than 10% of tumor mass, while the rest are normal inflammatory cells
- Arises primarily in a localized area of lymph nodes (neck, axilla, mediastinum), then spreads to anatomically adjacent LN group
- Mesenteric LNs and Waldeyer ring are rarely involved
- Bimodal age distribution (first peak in children, then in old age groups)
- B-symptoms: patients commonly have fever, night sweats and weight loss


CLASSIFICATION

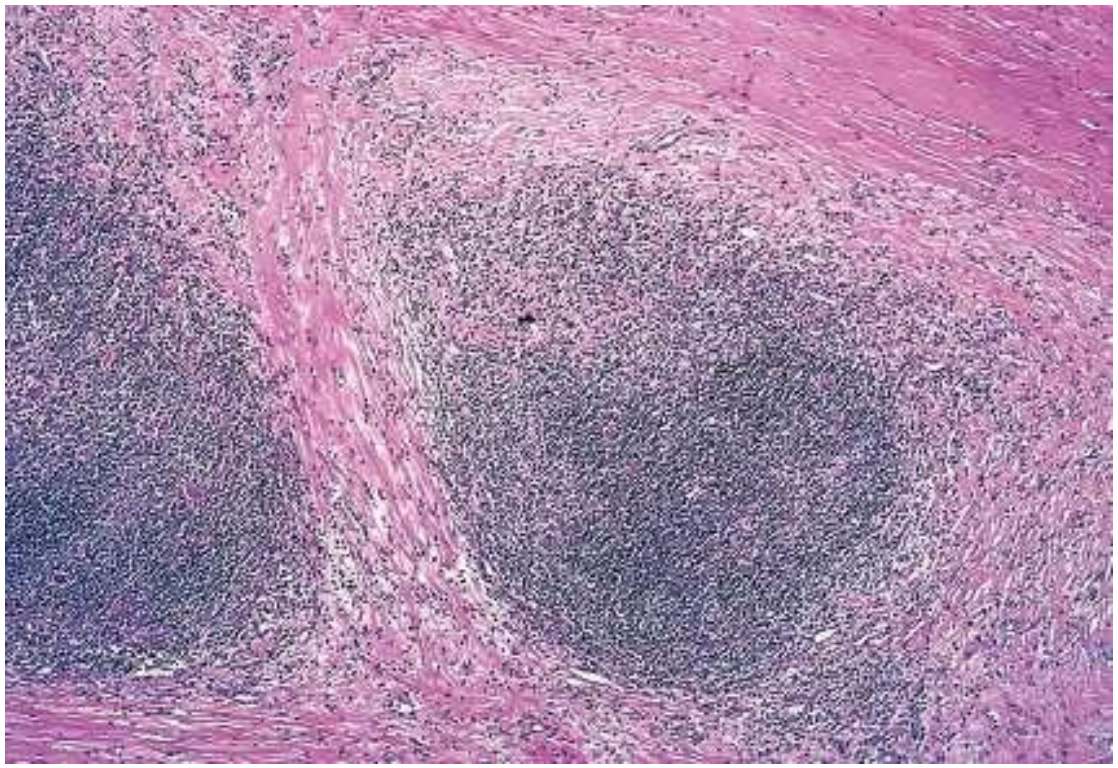
- Classic Hodgkin lymphoma (95%):
- 1) nodular sclerosis
- 2) mixed cellularity
- 3) lymphocyte-rich
- 4) lymphocyte-depleted

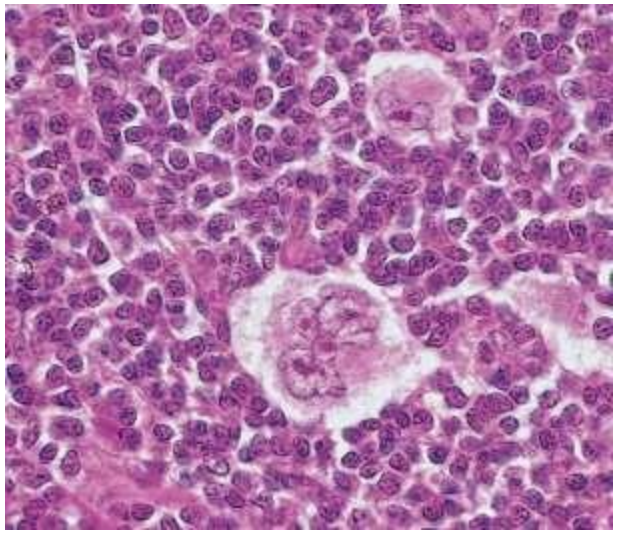
- Non-Classic Hodgkin (5%):
- Nodular lymphocyte-predominant



- Reed-Sternberg cells: bi or multi-nucleated giant cell, prominent nucleoli, abundant cytoplasm
- Hodgkin cells: mononuclear giant cell
- Both express CD30 and CD15, and negative for CD20, CD3 and CD45

NODULAR SCLEROSIS HL

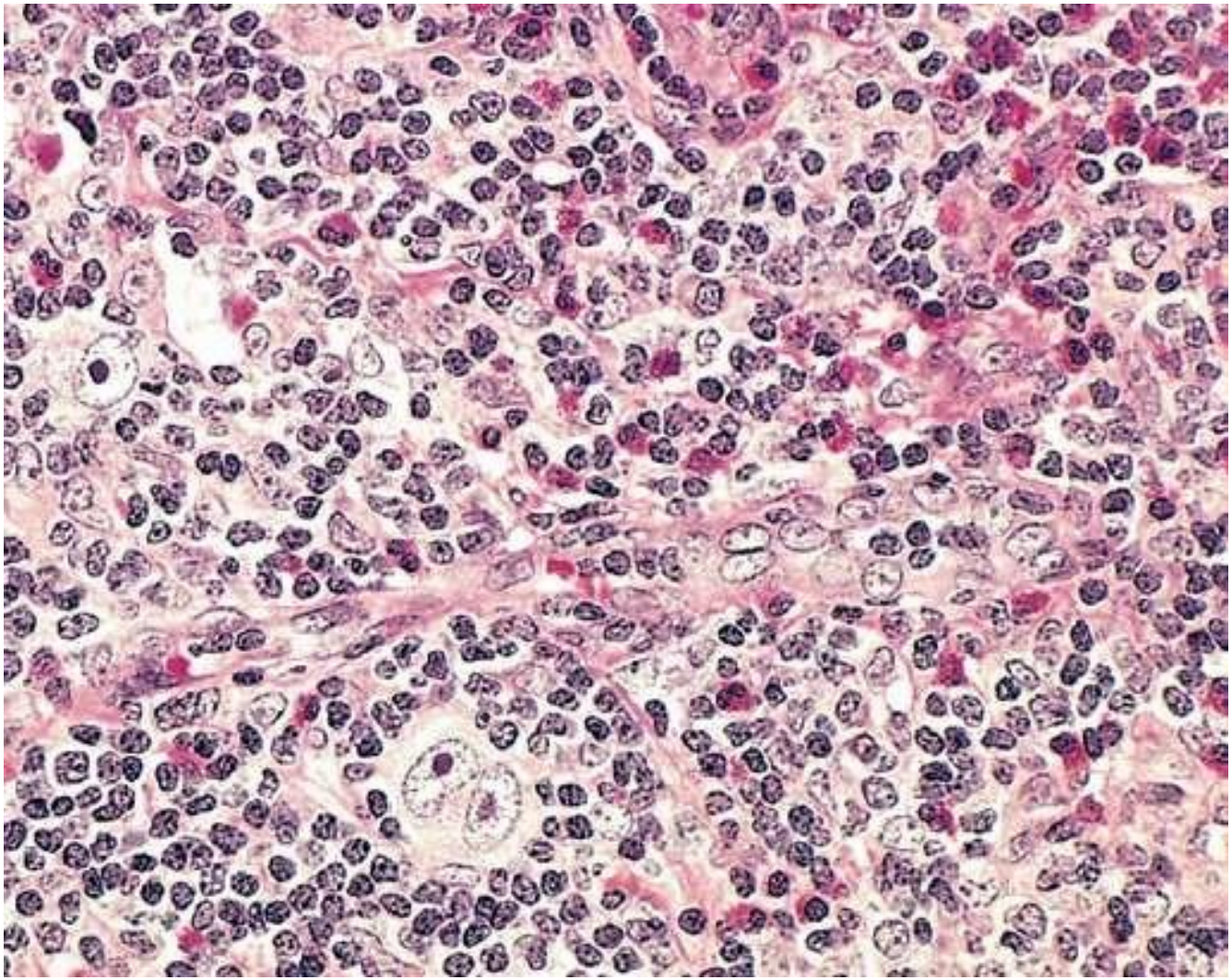




- Common in children and young adults
- Thick fibrous bands separating nodules of lymphocytes
- RS cells show clear cytoplasm, as a retraction artifact from formalin, called Lacunar cells

MIXED CELLULARITY HL

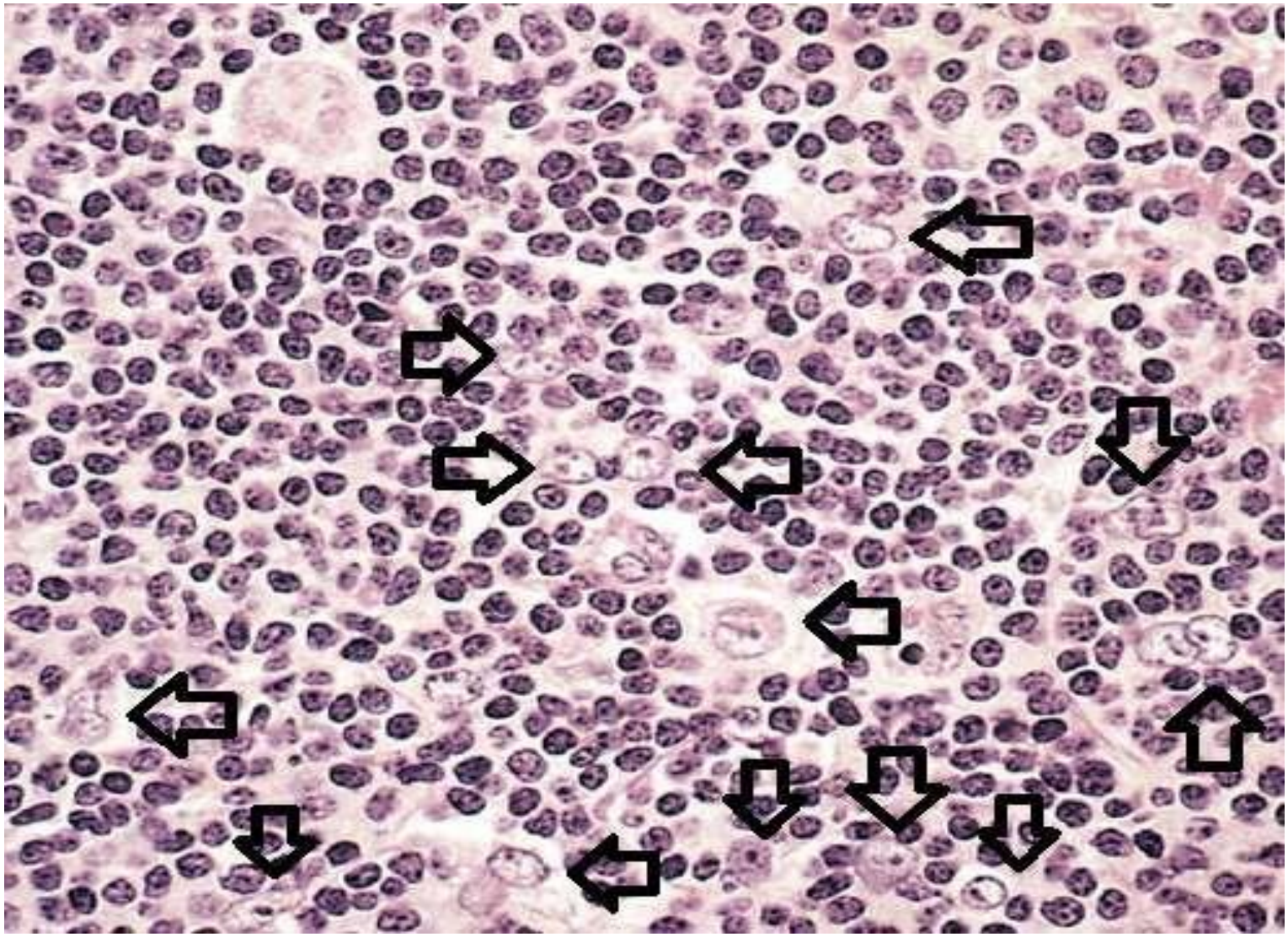
- Common in old people
- Numerous RS cells
- Lacks fibrous bands
- Associated with EBV
- Background: mixed neutrophils, eosinophils, lymphocytes, plasma cells and histiocytes



- Mixed cellularity HL

LYMPHOCYTE-PREDOMINANT HL

- Malignant cells are called lymphohistiocyte (L&H) variant RS cell, or simply LP cells
- Resemble popcorn (popcorn cells)
- Giant cell with multilobated vesicular nuclear lobes and small blue nucleoli
- Express normal B-cell markers (CD45, CD20), negative for CD30 and CD15
- Background of lymphocytes, arranged in nodules
- Excellent prognosis



- Popcorn cells

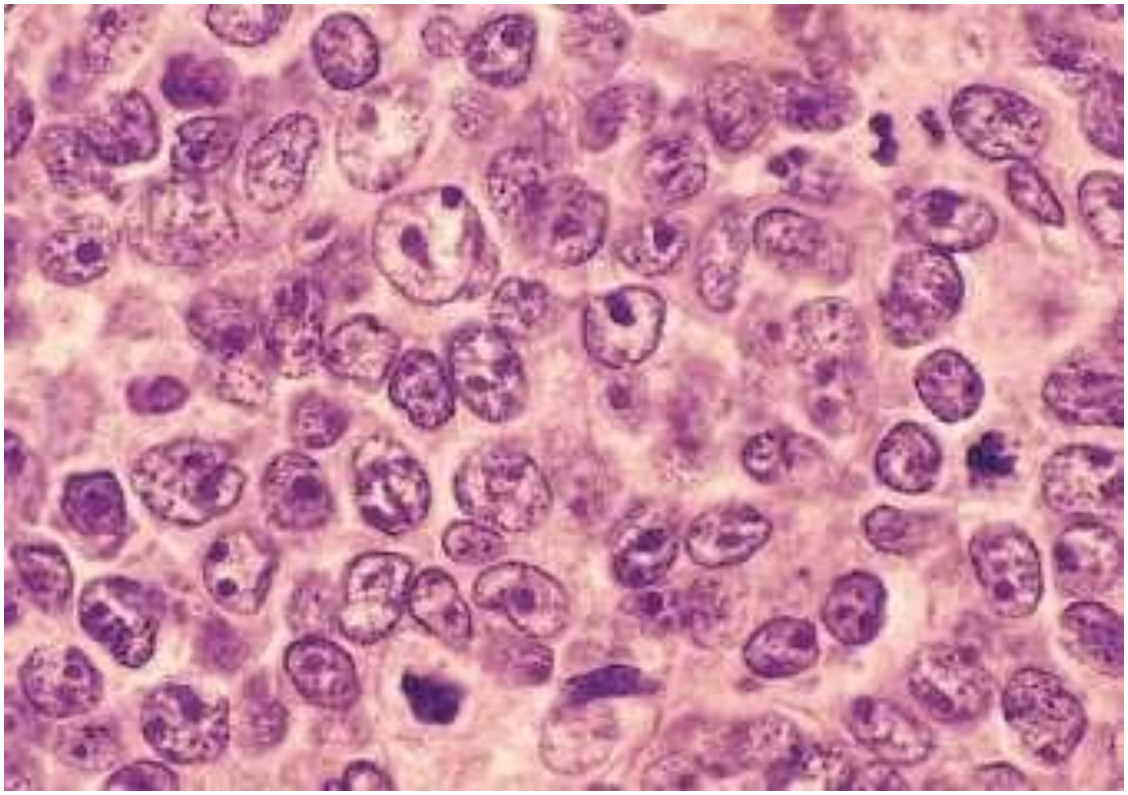
PATHOGENESIS AND OUTCOME

- Originate from germinal center B-cells
- Frequent association with EBV
- RS cells secrete IL-5, chemoattractant for eosinophils
- Also secrete IL-13 and transforming growth-B (TGF-ß) which activates other RS cells
- Express programmed death (PD) ligands which antagonize T cell response, escaping immune surveillance
- Prognosis is generally good

DIFFUSE LARGE B-CELL LYMPHOMA

- Most common NHL
- Predominantly in adults
- High-grade (rapidly growing mass)
- Most common non-cutaneous extranodal lymphoma (GI most common)
- 2/3 have activating mutation of Bcl6 promotor gene, which is an important regulator of gene expression in germinal center B-cells
- 30% have t(14;18) (Bcl2 IgH) which results in overexpression of Bcl2 protein (anti-apoptotic)
- Few has mutation in MYC gene

MORPHOLOGY



- DLBCL: cells are large (3x normal lymphocytes), irregular nuclei, small nucleoli, frequent mitosis. Positive for CD20

DLBCL-SUBTYPES

- Most cases arise de novo, few complicate a previous low-grade B-cell lymphoma
- Primary mediastinal large B-cell lymphoma: arises from thymic B-cells, most patients are middle age women, spread to CNS and visceral organs
- EBV-associated DLBCL: arise in immune suppressed patients and in elderly, begin as polyclonal B-cell proliferation
- Human Herpes Virus-8: causes DLBCL in pleural cavity, encodes cyclin D1 mimicker protein, seen in immune suppressed patients

FOLLICULAR LYMPHOMA

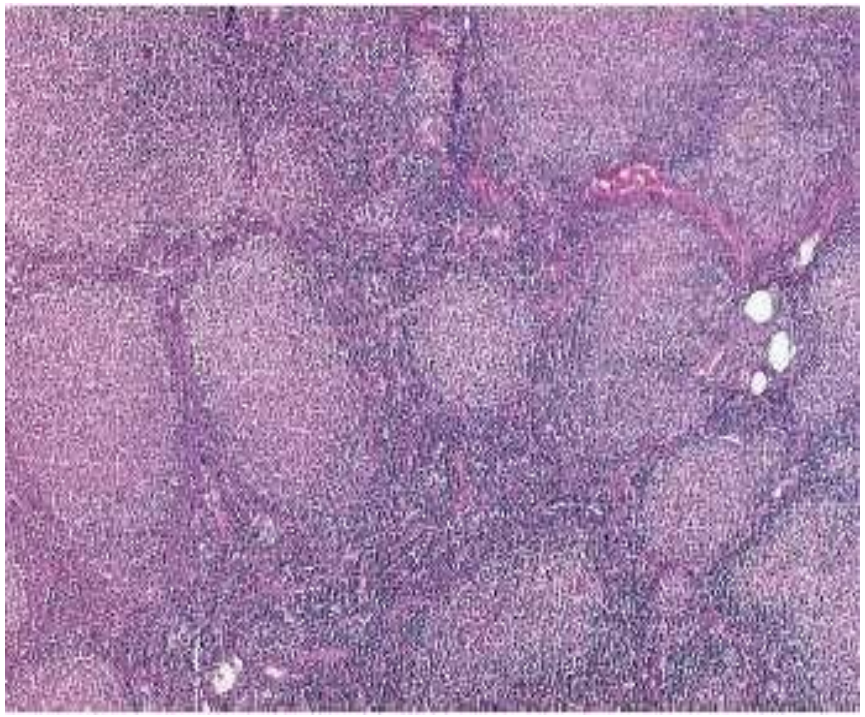
- Second most common NHL
- Common in the West (less in Asian countries)
- Mainly in > 50 years
- M>F
- Patients present with generalized lymphadenopathy
- Commonly disseminates to BM, liver and spleen (80%)

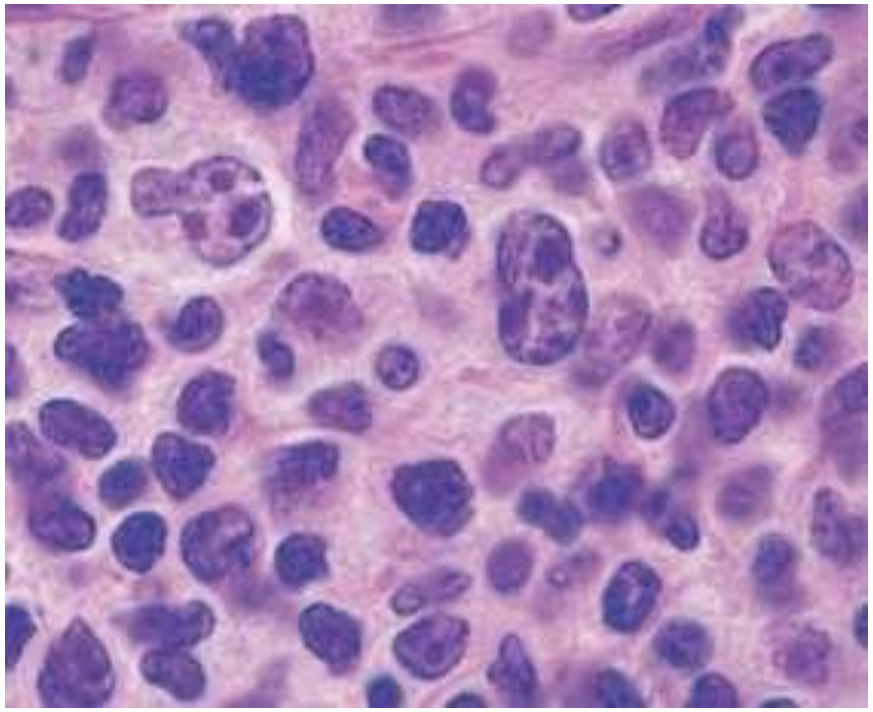
PATHOGENESIS

- t(14;18) (Bcl2□IgH)
- Overexpression of Bcl2 results in prolonged survival of lymphoma cells
- 1/3 of patients have mutations in genes encoding histone-modifying proteins (epigenetic change)

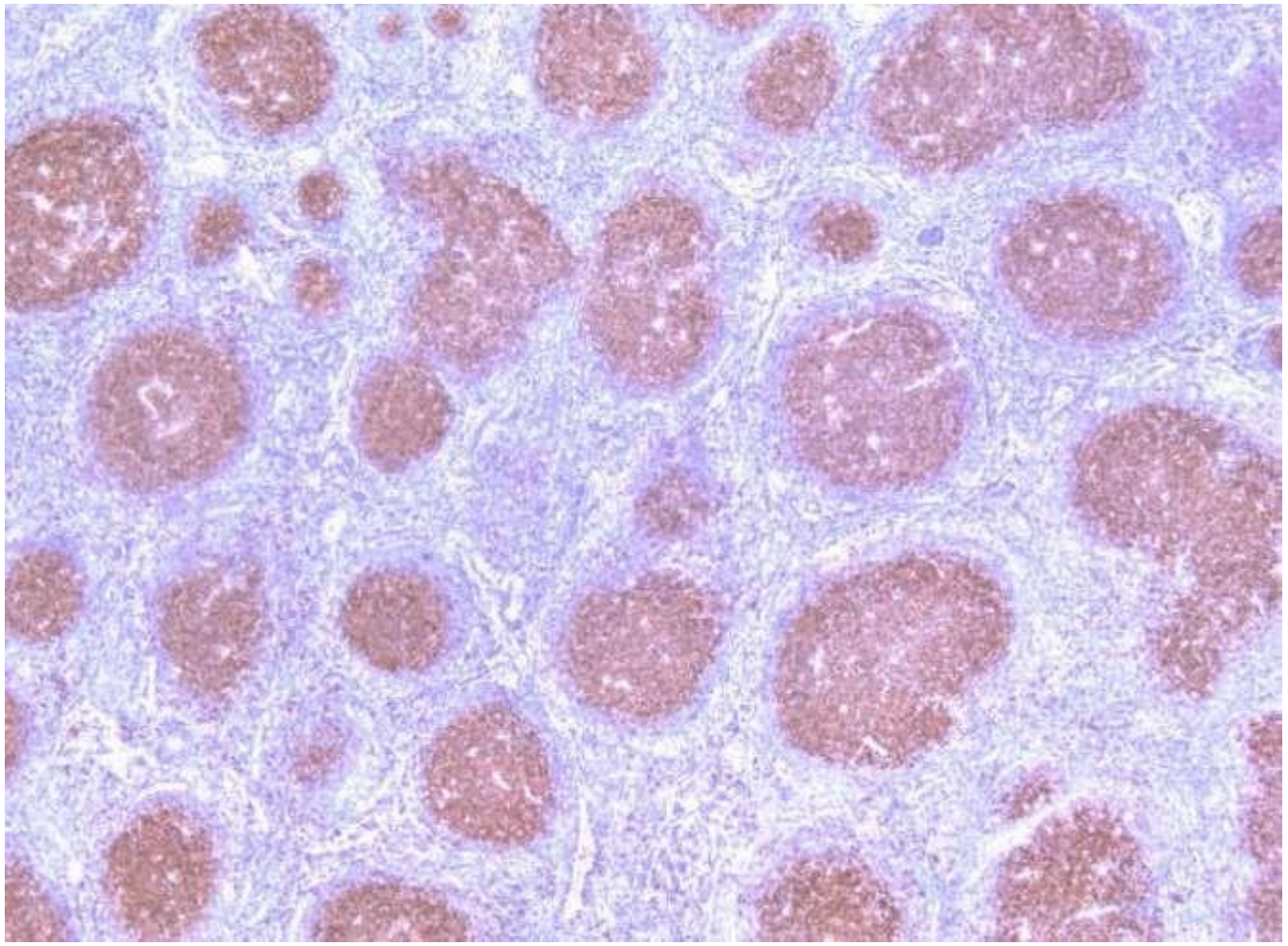
MORPHOLOGY

- The normal architecture of lymph node is effaced by nodular proliferation (follicles)
- The follicles are composed of small irregular "cleaved" lymphocytes "centrocytes" and large lymphocytes with vesicular nuclei and small nucleoli (centroblasts)
- In most cases, the centrocytes predominate (low-grade). With time, centroblasts increase and the disease becomes high-grade
- Cells express CD20, Bcl2, Bcl6





- Morphology of FL, left: nodular (follicular growth of neoplastic cells effacing the entire lymph node architecture. Right: most cells in this field are centrocytes, appear as small fark cells with cleaved nuclei. There are few large cells with multiple nucleoli, corresponding to centroblasts



- Bcl2 immunohistochemical stain is positive in follicles in follicular lymphoma

PROGNOSIS

- Indolent course
- Conventional chemotherapy is ineffective
- Overall median survival is 10 years
- 40% develop transformation to DLBCL (worse than de novo DLBCL)
- Therapy is reserved to symptomatic patients, bulky tumors and transformation (cytotoxic chemotherapy, anti-CD20, anti-Bcl2)

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

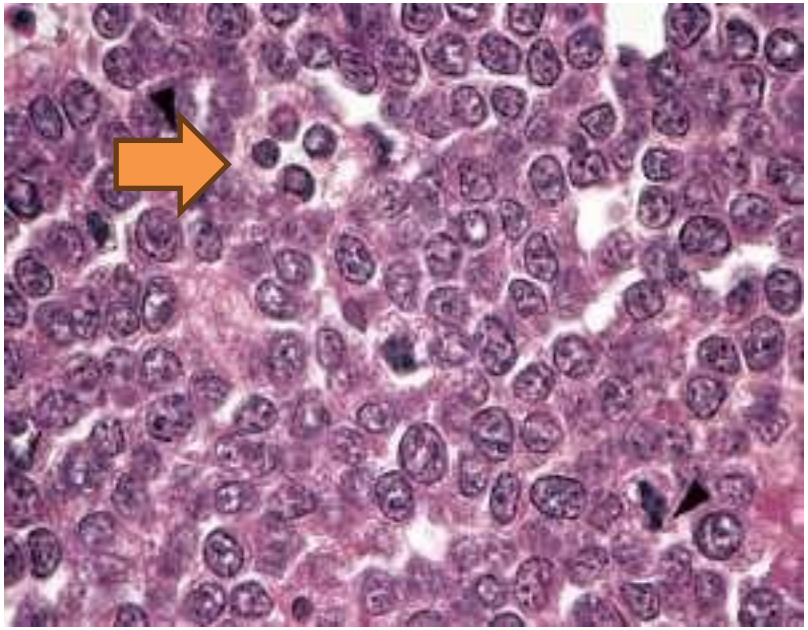
- Extranodal disease: jaw (endemic), terminal ileum, retroperitoneum, ovary, CNS (sporadic), sometimes leukemic

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, tingible body macrophages engulfing nuclear debris



Extranodal 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

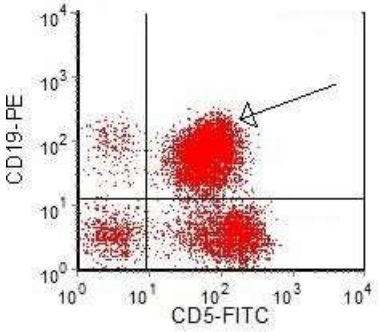
- Arises from naïve B-cells in mantle zone
- Most commonly in older men
- t(11;14) that fuses cyclin D1 gene to IgH locus
- Overexpression of cyclinD1, promote progression of cell cycle
- Affects LNs, Waldeyer ring
- Commonly involve BM, blood in 20%, sometimes in GIT, appears as submucosal nodules (lymphomatoid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

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

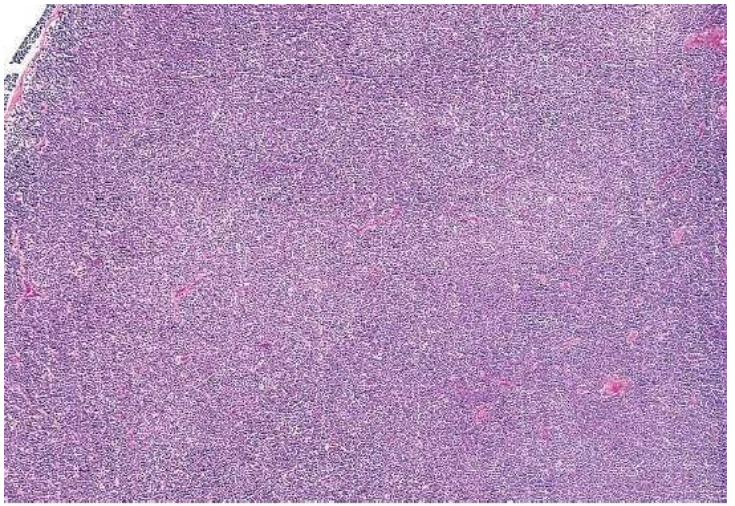

PATHOGENESIS

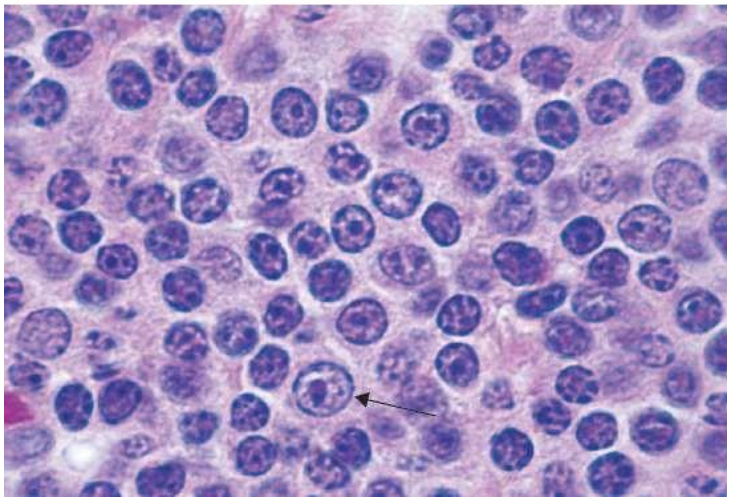
- Increased Bcl2 protein, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators of Bcl2
- A surface immunoglobulin called B-cell receptor (BCR), is autonomously active, activating a intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell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



MORPHOLOGY OF SLL

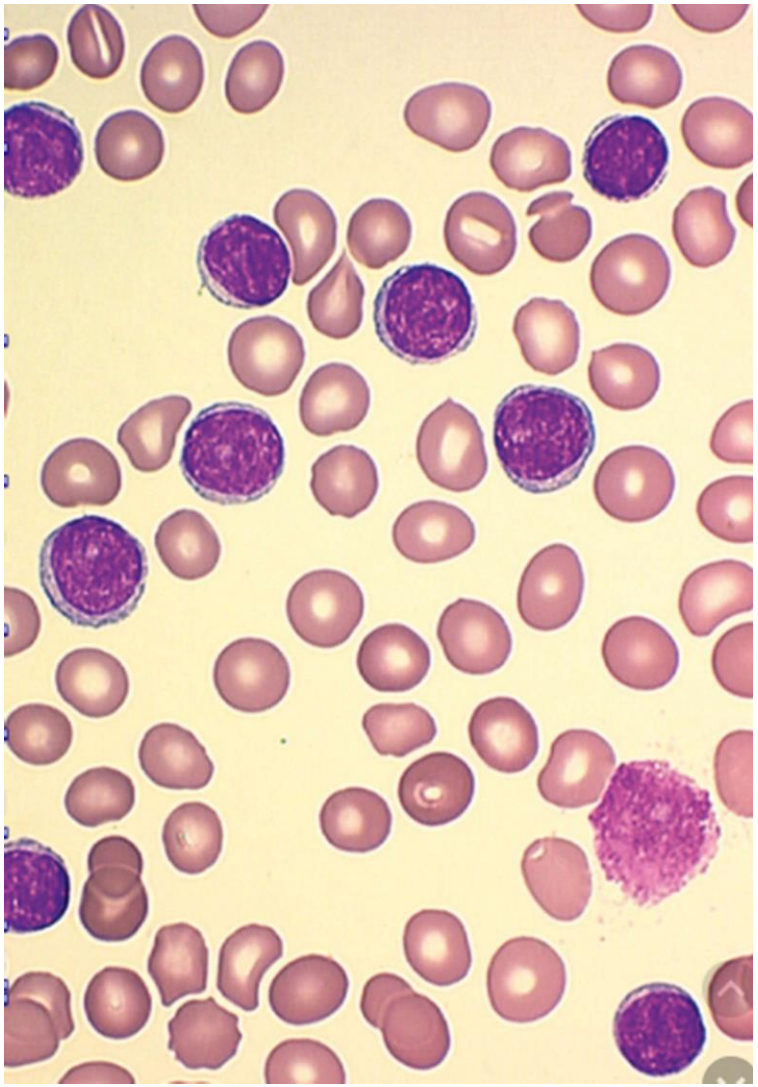
- LN shows effacement of architecture
- Most of neoplastic cells are small in size, round, dark chromatin, along with few large cells with central prominent nucleolus (prolymphocyte)
- Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis





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

PLASMA CELL MYELOMA

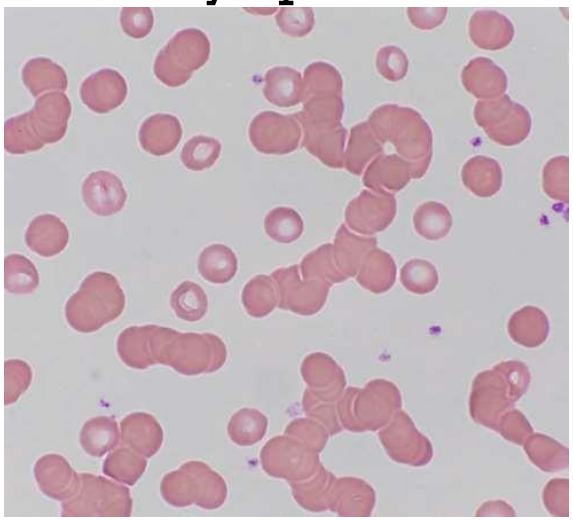
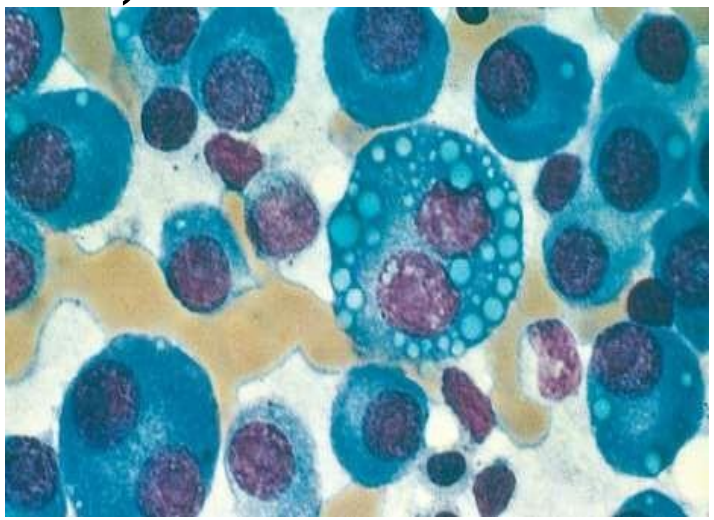
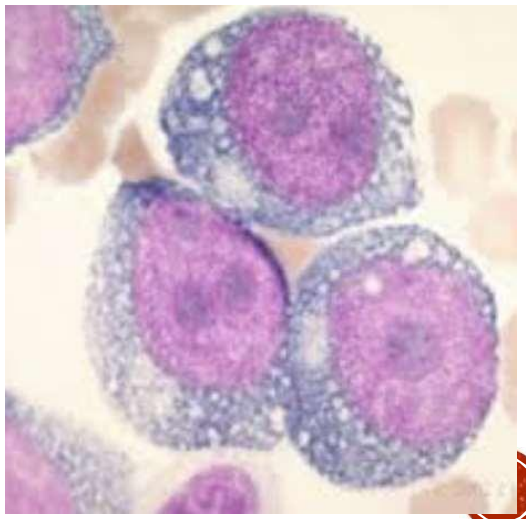
- AKA multiple myeloma
- Common neoplasm
- Commonly in elderly, more common in men, African origin
- Malignant plasma cells secrete monoclonal protein (M protein), most commonly IgG (60%), then IgA (20-25%), followed by other types.
- Sometimes only light chain (kappa or lambda), can be detected in urine (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)
- Morphologically might resemble normal plasma cells, or become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles)

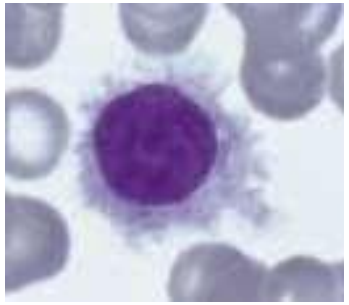




CLINICAL AND LABORATORY FINDINGS

- 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

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

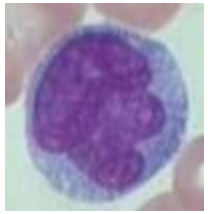


PERIPHERAL T-CELL LYMPHOMA

- 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
- 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