PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM–7

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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

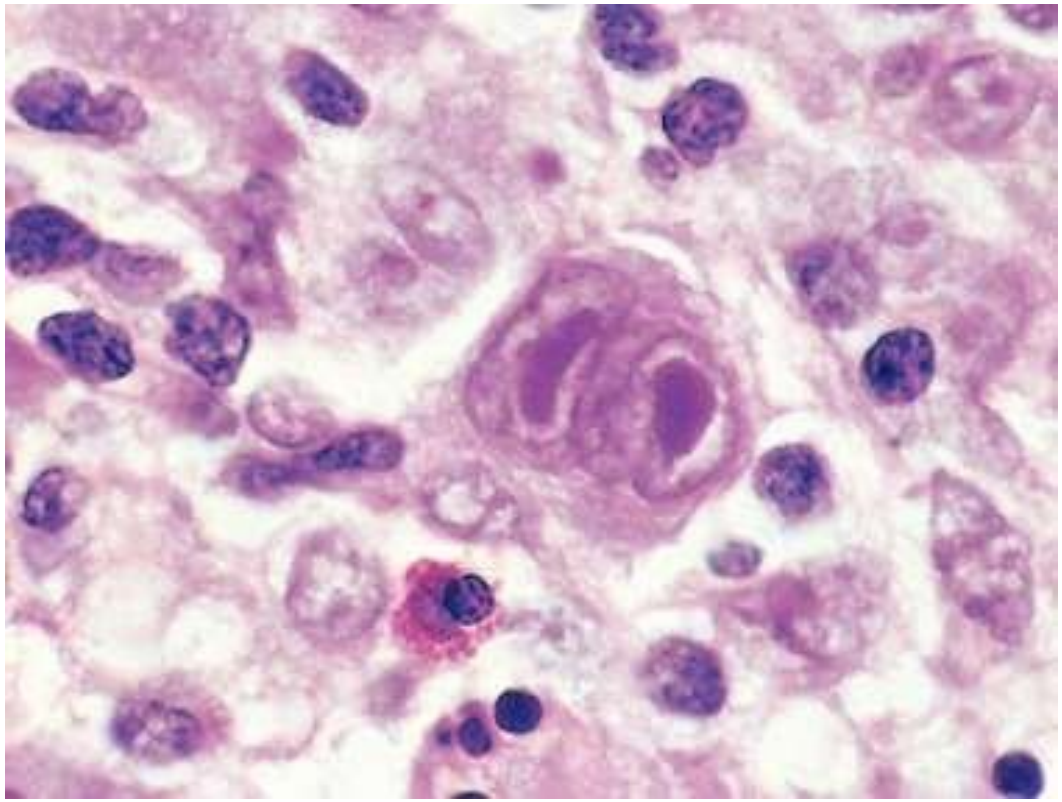
HODGKIN LYMPHOMA

- 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

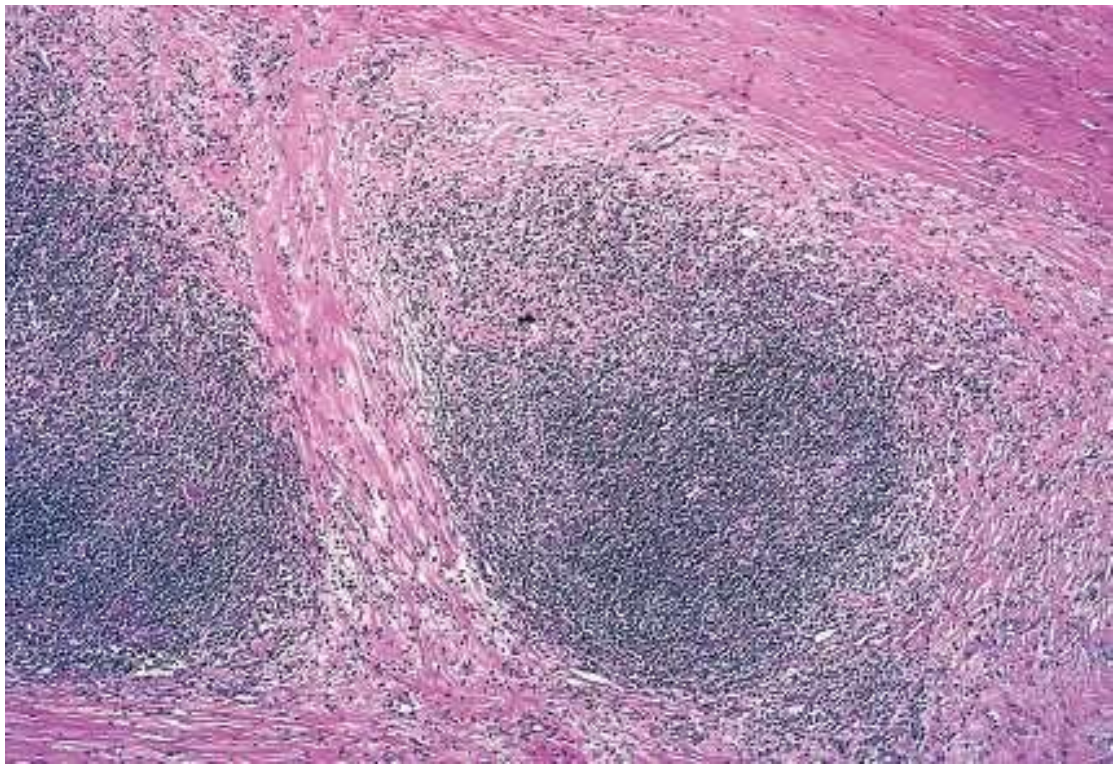
- Classic Hodgkin lymphoma (95%):
- 1) nodular sclerosis
- 2) mixed cellularity
- 3) lymphocyte-rich
- 4) lymphocyte-depleted

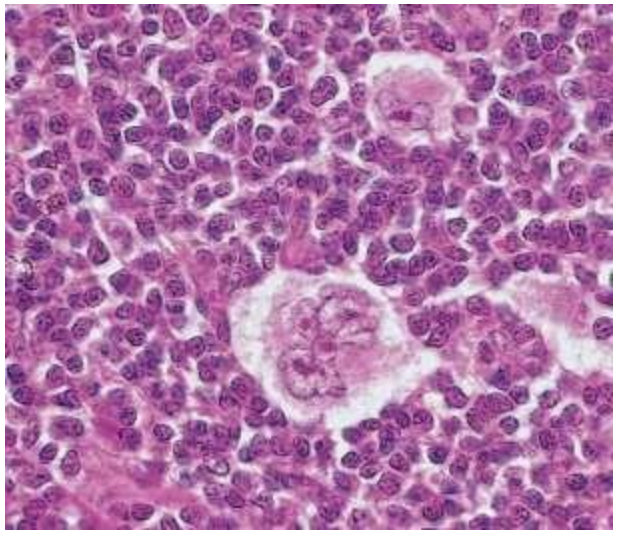
- Non-Classic Hodgkin (5%):
- Nodular lymphocyte-predominant



- 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

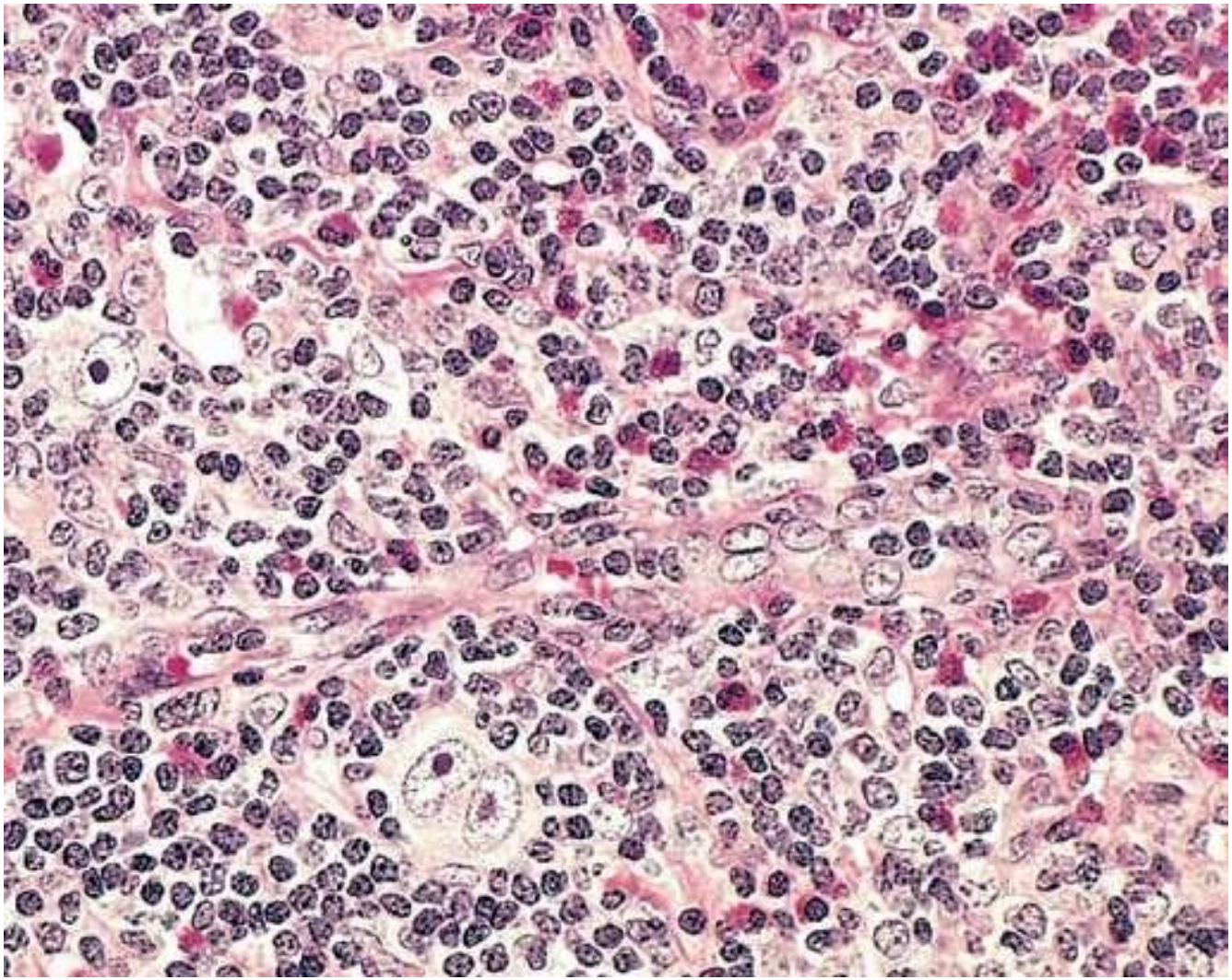




- Common in children and young adults
- Thick fibrous bands separating nodules of lymphocytes
- RS cells show clear cytoplasm, as a retraction artifact from formalin, called Lacunar cells

MIXED CELLULARITY HL

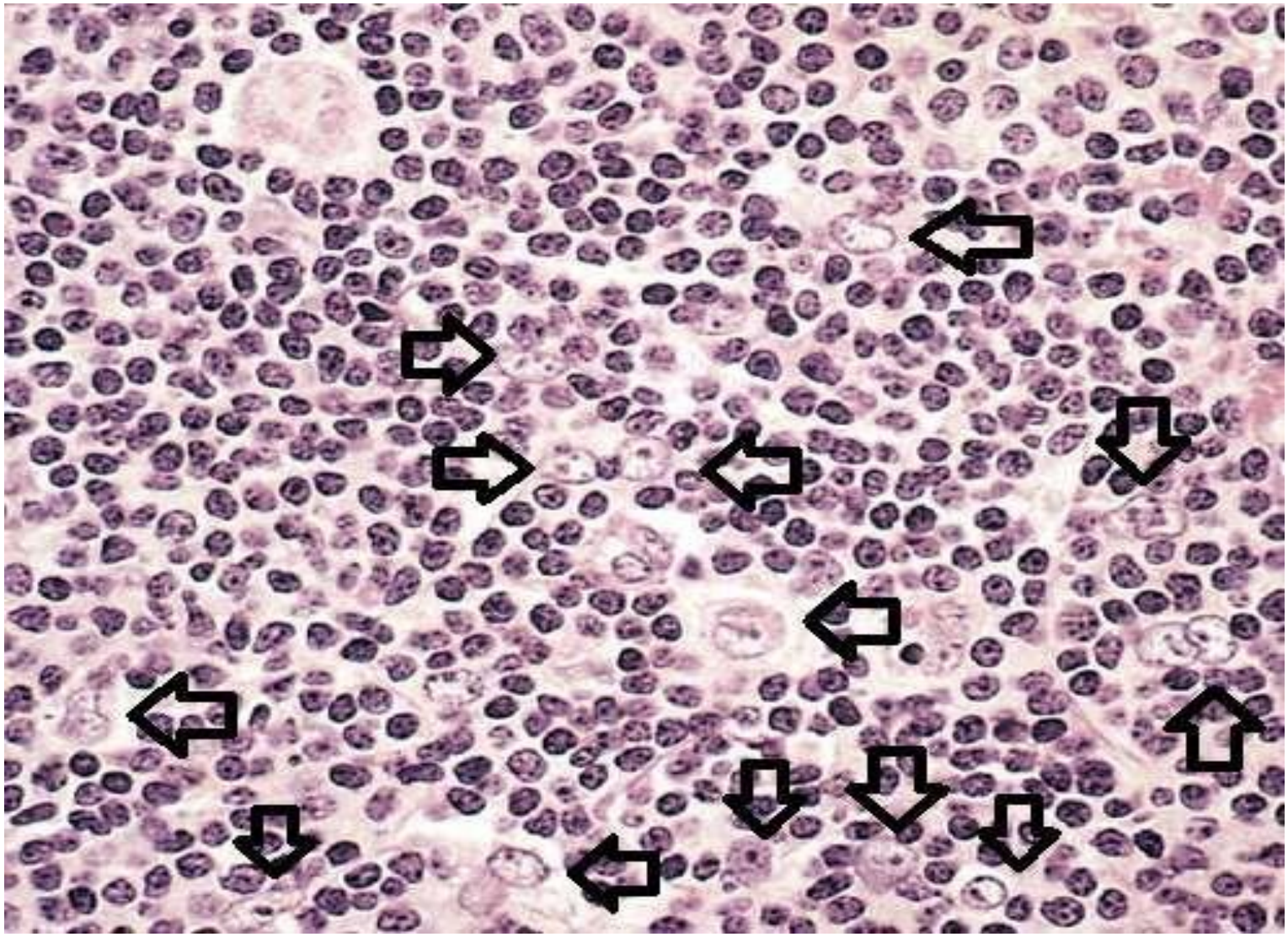
- Common in old people
- Numerous RS cells
- Lacks fibrous bands
- Associated with EBV
- Background: mixed neutrophils, eosinophils, lymphocytes, plasma cells and histiocytes



- 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

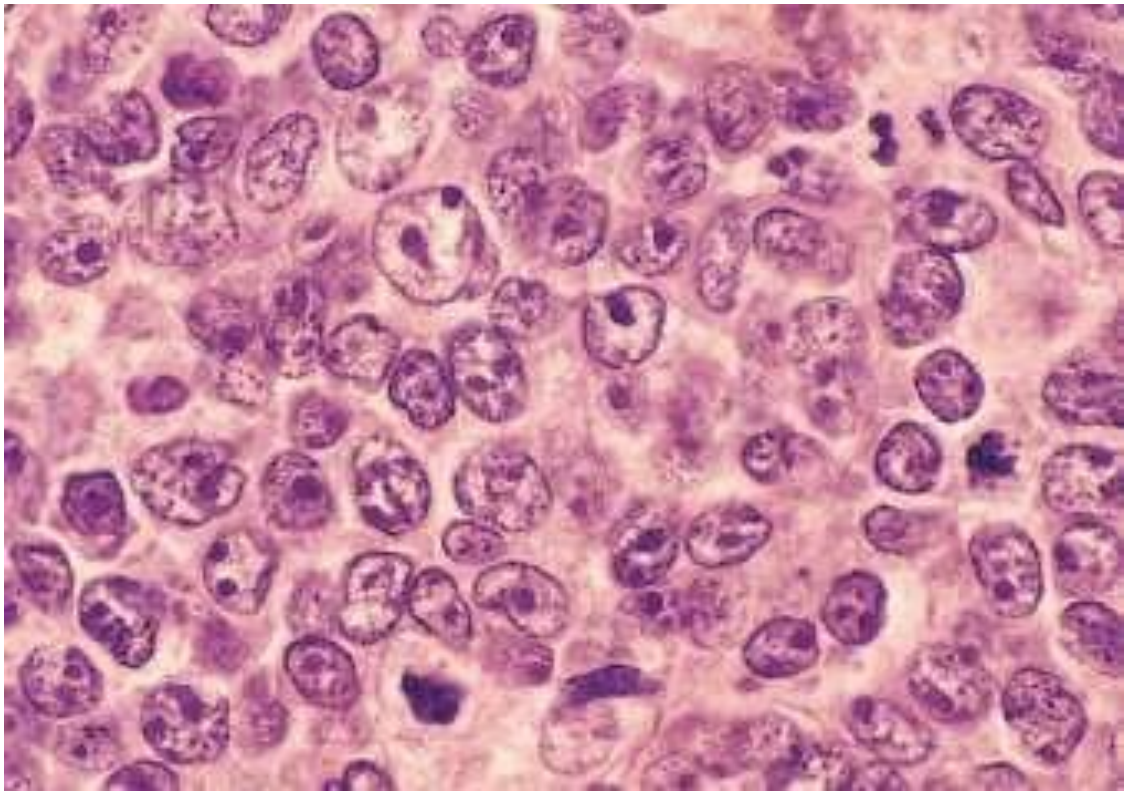
PATHOGENESIS AND OUTCOME

- 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

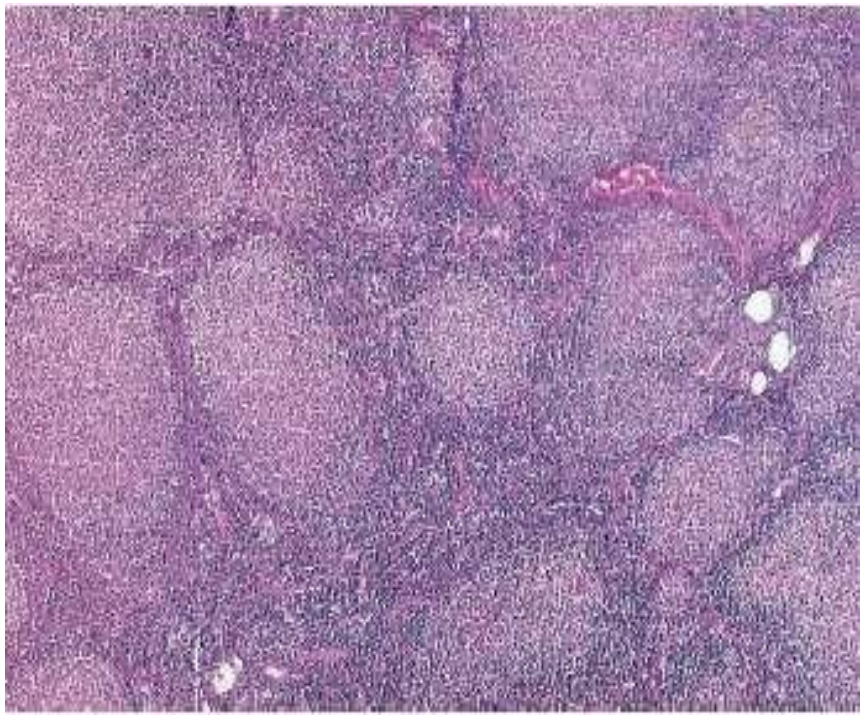
- Second most common NHL
- Common in the West (less in Asian countries)
- Mainly in > 50 years
- M>F
- Patients present with generalized lymphadenopathy
- Commonly disseminates to BM, liver and spleen (80%)

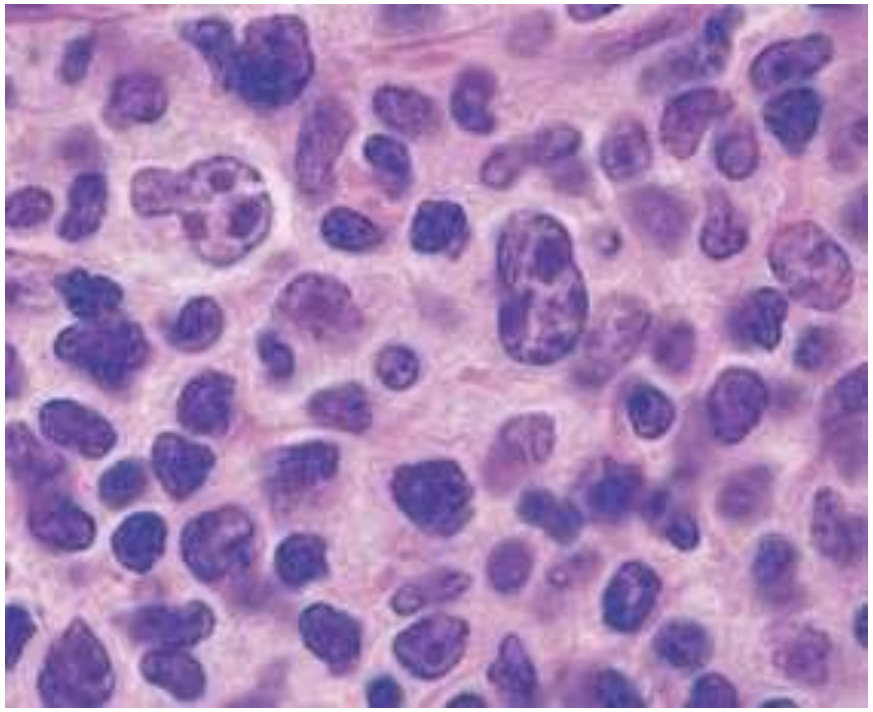
PATHOGENESIS

- 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)

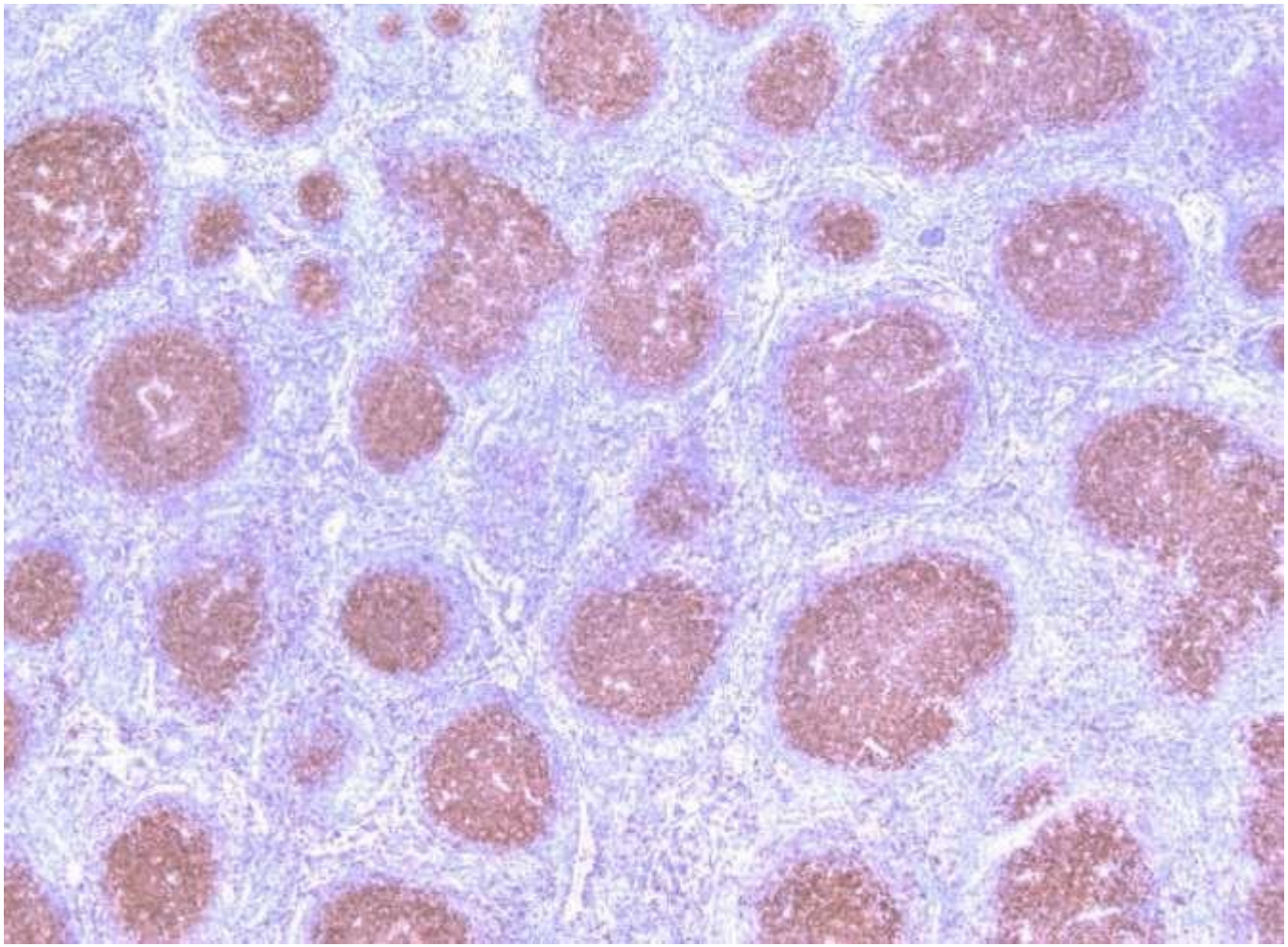
MORPHOLOGY

- 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)