Lymph node pathology II - Lymphoma

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DEPARTMENT OF PATHOLOGY

Cytology of the lymph node

Composed of

- Transient B and T lymphocytes
- Antigen processing and presenting cells
- Replicating B and T lymphocytes (in response to antigen)
- Persistent and transient final effector cells
- Macrophages

Some of these functional subgroups are cytologically unique, others cytologically indistinguishable

Cell types – small lymphocytes

Small round nucleus with clumped chromatin, small or absent nucleolus scanty cytoplasm.

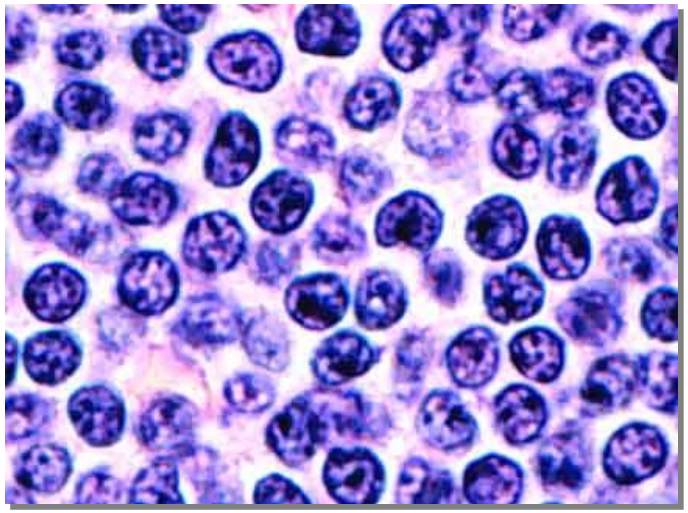
Can be T or B cell, virgin (unexposed to antigen) or differentiated effector/memory cell.

Most likely lineage, B or T, guessed by location within the node, but lineage and state of differentiation must be confirmed by immunologic/molecular techniques

B cells- primary follicles, mantle zone of secondary follicles, medullary cords

- T cells- paracortex, minor population within germinal center.

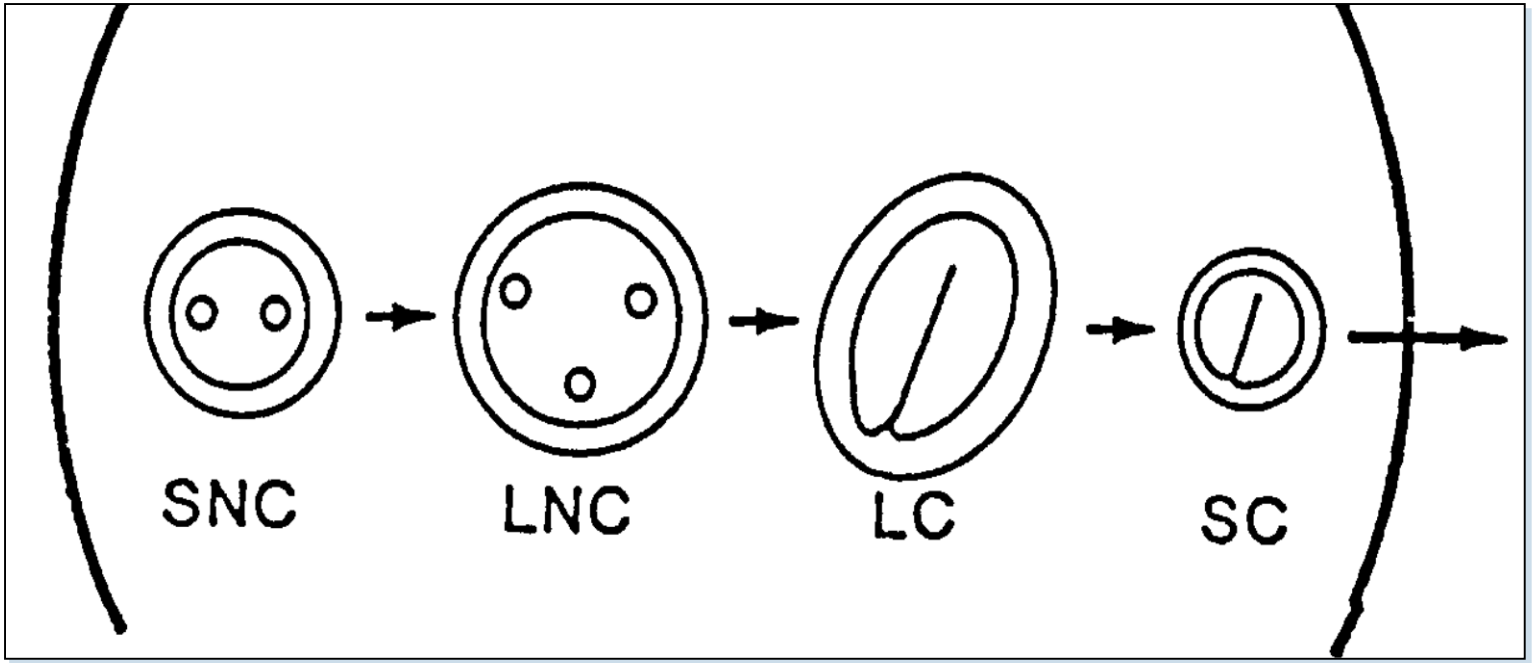
- *Clumped chromatin -cell is not proliferating- not activated to enter the cell cycle and replicate*



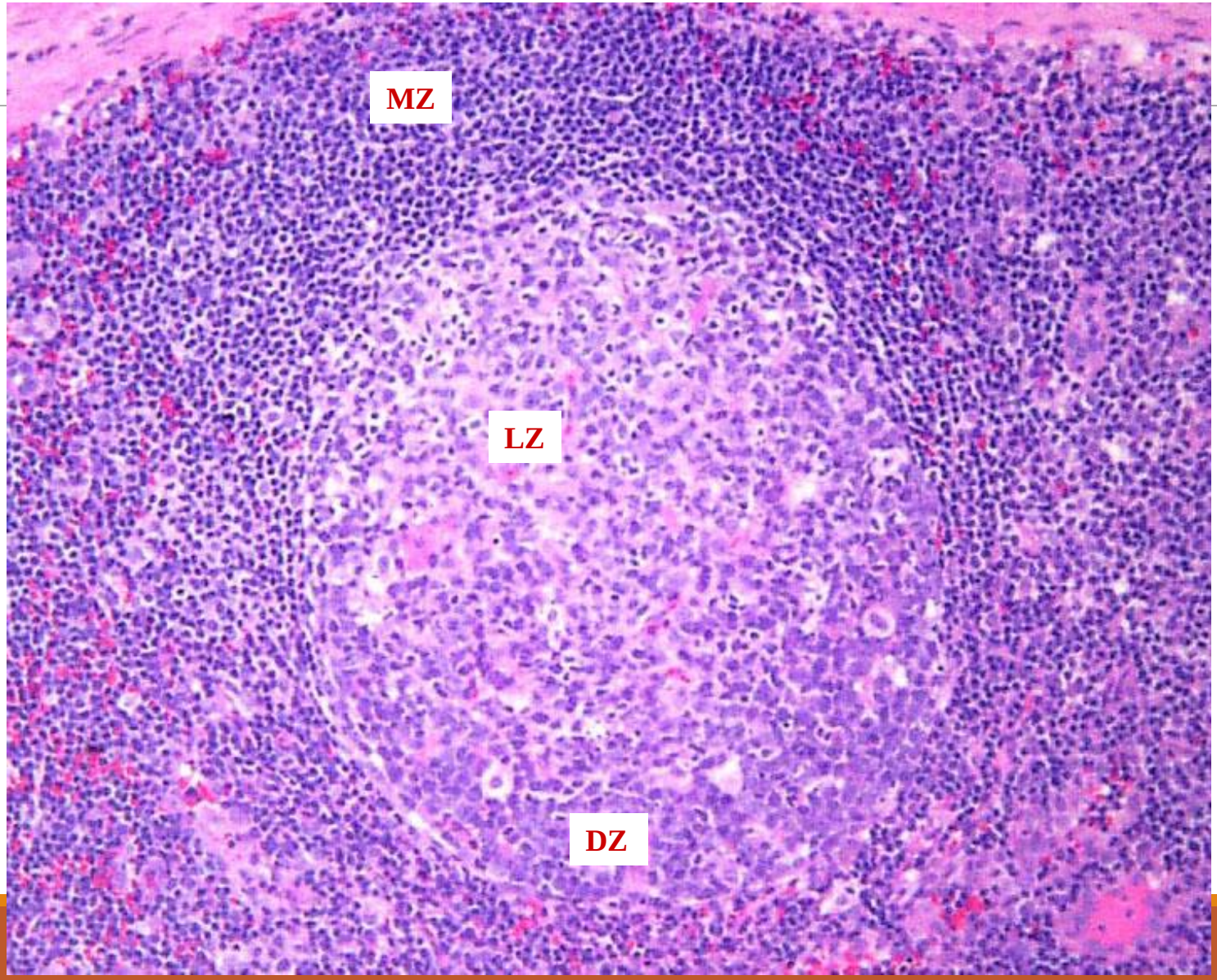
Cell types : Follicular center cells

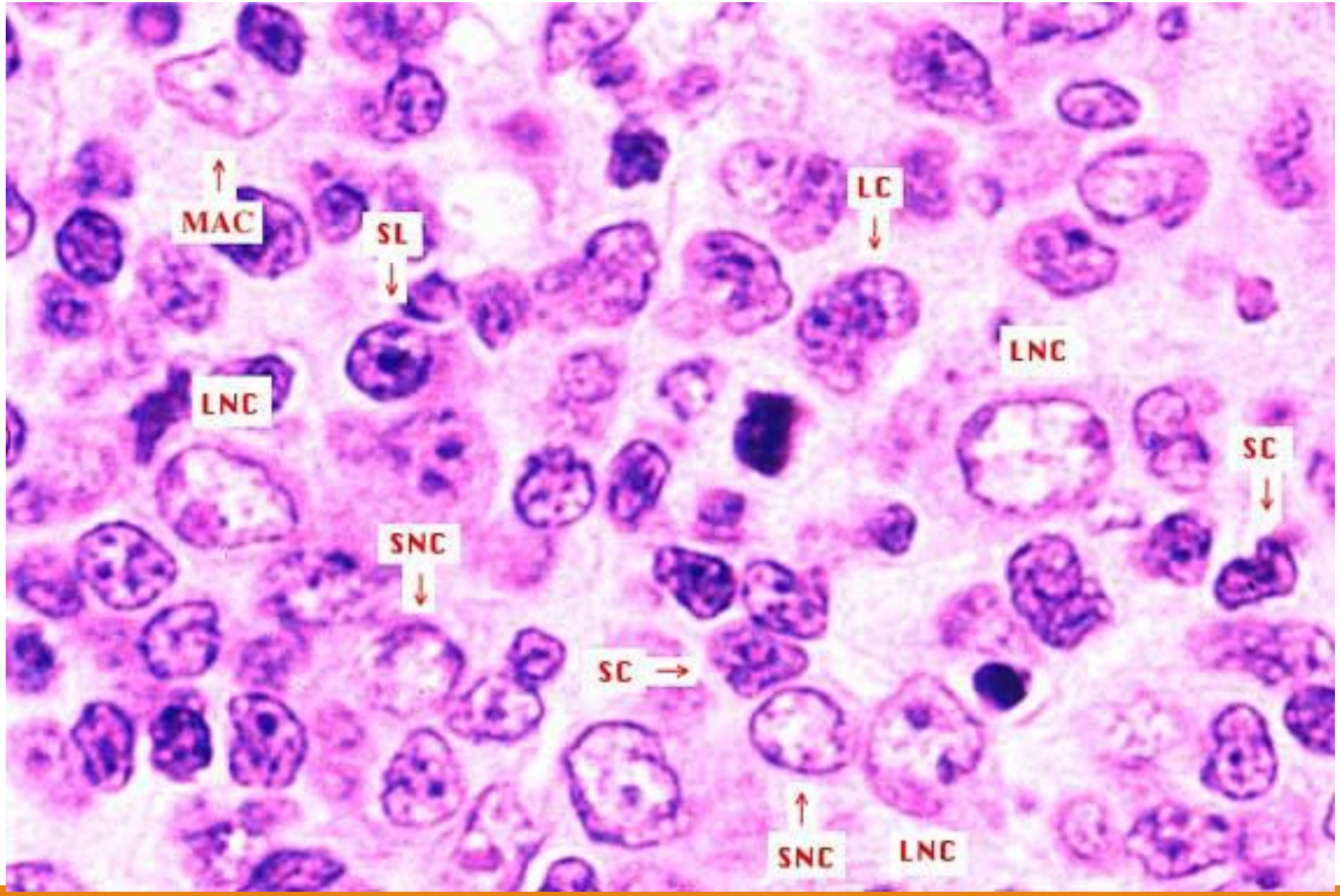
Replicating and post-replicating B cells

- **Noncleaved cells, small and large**
  - **Replicating** populations- expanding antigen responsive cells.
  - Round nuclei but larger than resting small lymphocyte
  - Open or vesicular chromatin
  - Recognizable nucleoli.
    - Nucleus clear -->genetic material unwound for replication.
  - Size, large or small compared to nucleus of macrophage.
- **Small cleaved cells-**
  - **Nonreplicating** population
  - Post mitotic memory or plasma cell precursors
  - Clumped chromatin
  - Irregular folded and cleaved nuclear profiles


SNC
LNC
LC
SC

Reactive germinal center




MAC
SL
LC
LNC
LNC
SC
SNC
SC
SNC
LNC

Cytology of the lymph node

Immunoblasts

- Replicating large cells found outside the germinal centers.
- May be of B or T cell type
- Have nuclear characteristics of replicating lymphocytes-
  - Vesicular chromatin
  - Nucleoli

Accessory cells (Antigen processing cells)

- Interdigitating reticulum cells- T cell paracortex
- Dendritic reticulum cells- B cell germinal centers
- Process and present antigen to B and T lymphocytes
- Invisible in normal lymph node

Cytology of the lymph node

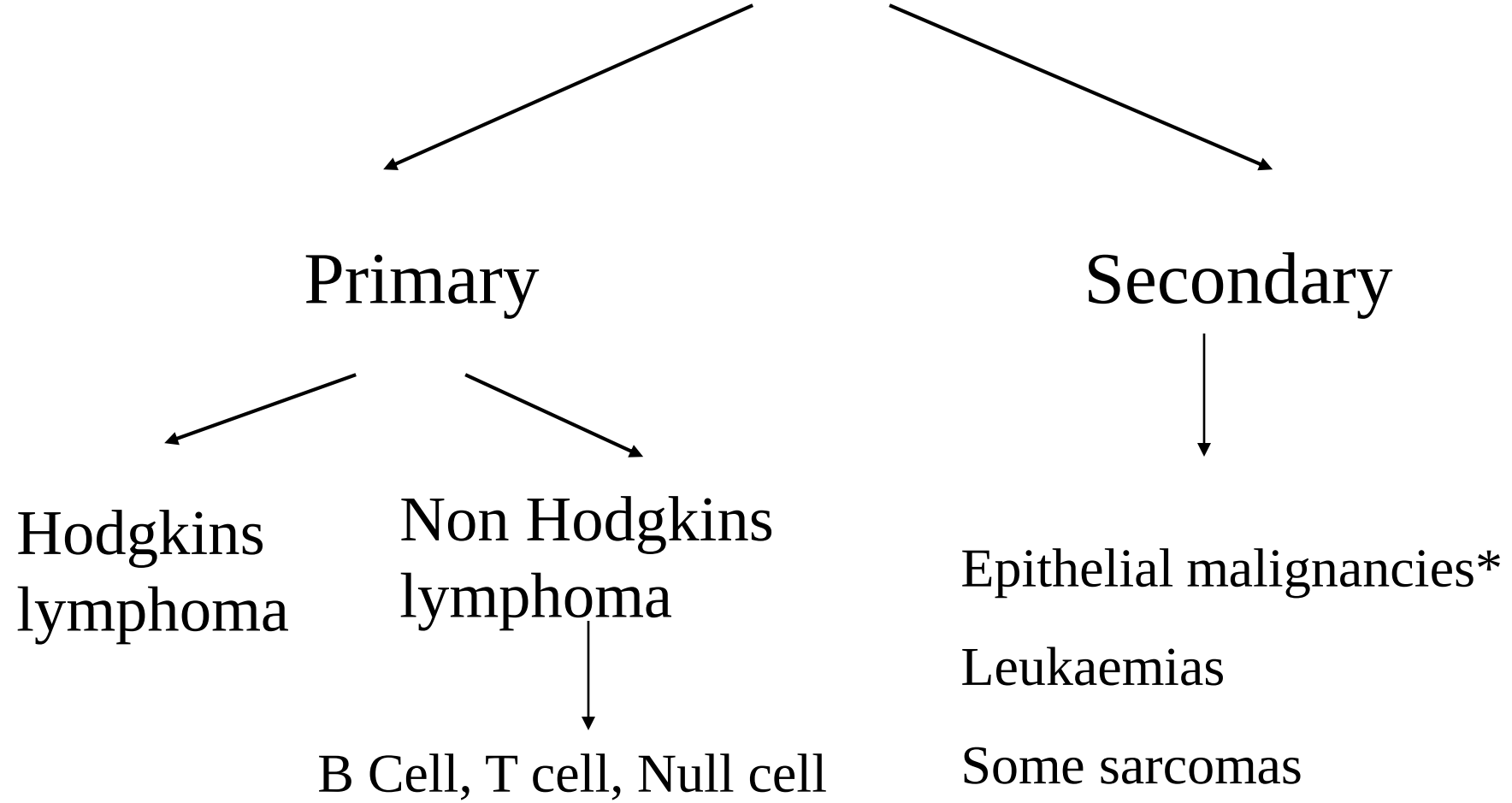
Macrophages (histiocytes)-

Abundant pale cytoplasm

Oval nucleus, single small nucleolus

- Examples:
  - Phagocytic cells of lymph node
  - Tingible body macrophages of germinal centers
  - Medullary and subcapsular sinus macrophages-

Causes of lymphadenopathy (Neoplastic)



Hodgkins lymphoma

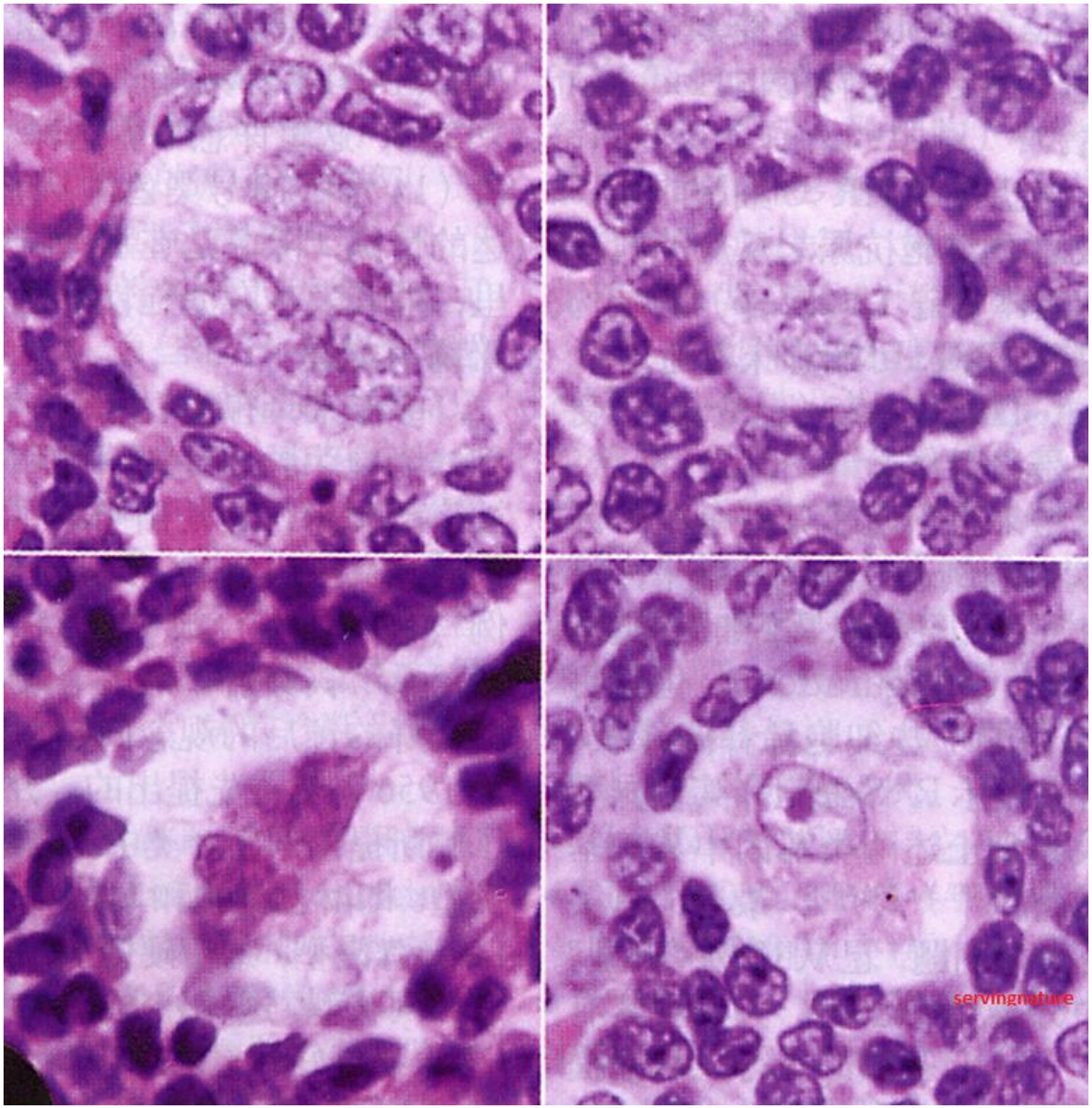
Presence of Reed - Sternberg cells in a background of non neoplastic cells

Presence of lymphocytes, plasma cells, eosinophils and polymorphs in the background. (mixed)

Nodular lymphocyte predominance

Classical types

- Lymphocyte rich
- Nodular sclerosing
- Mixed cellular
- Lymphocyte depleted.


servingnature

Nodular lymphocyte predominance Hodgkin lymphoma

Incidence – approximately 5% of HL

Usually young and middle aged: Median age 35yrs

Clinically well.

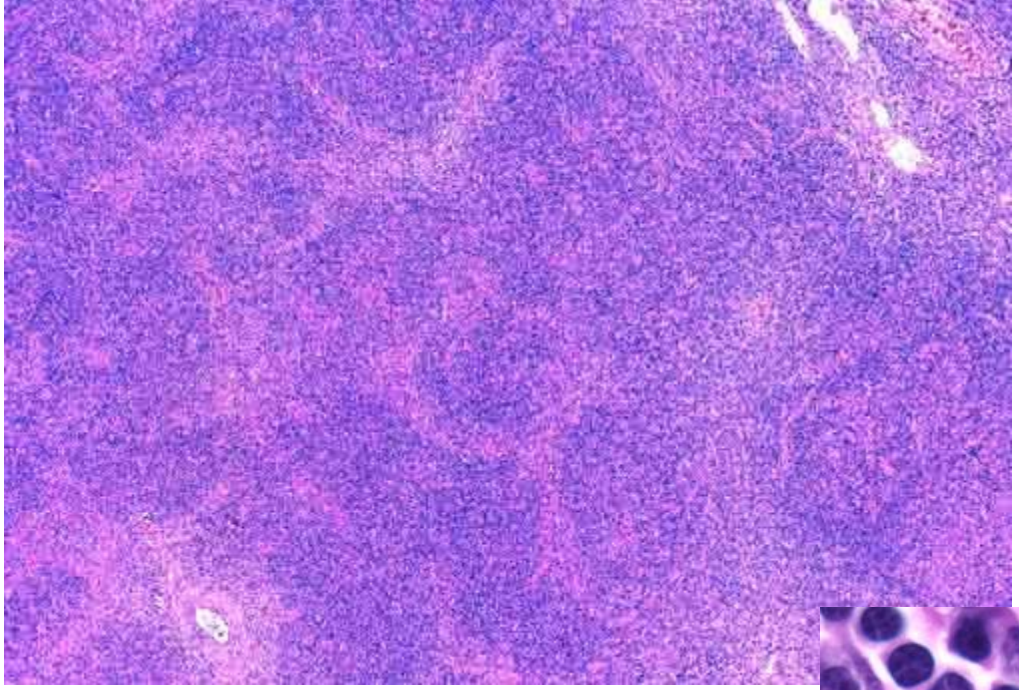
Lymphadenopathy of long duration.

- Typically affecting a single peripheral node

Presents in Stage I and II (80%)

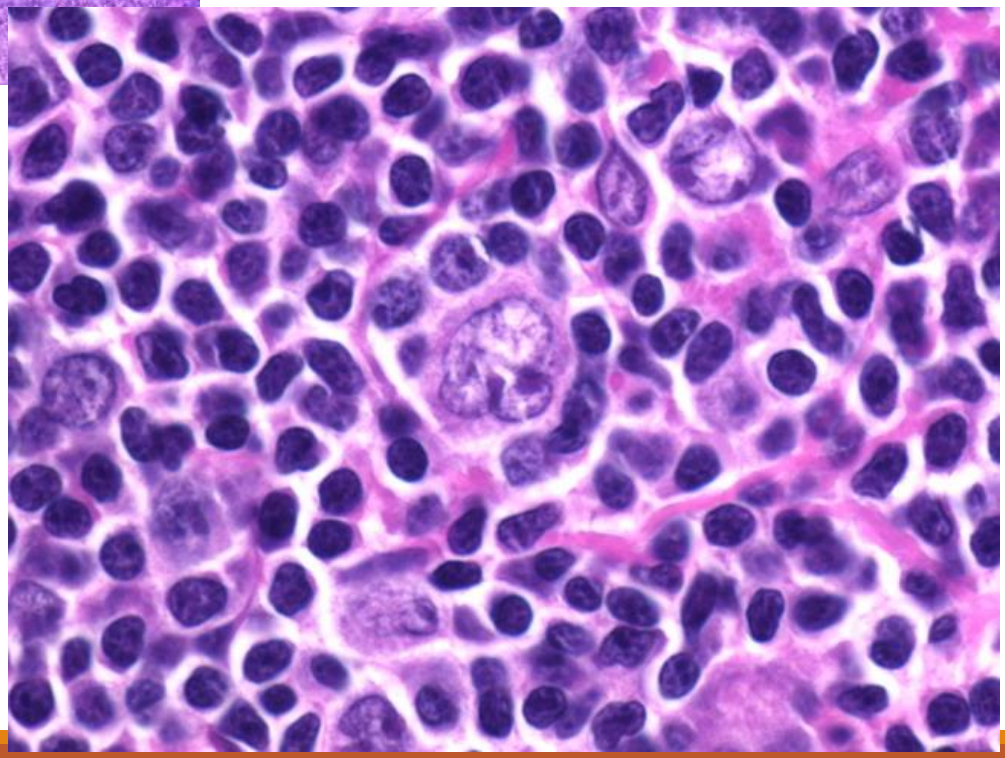
Microscopy;

- Nodular appearance
- Typical Reed Sternberg cells absent
- L & H cells – Pop corn cells with lobated folded nuclei and inconspicuous nucleoli
- Inflammatory background – lymphocytes and histiocytes only



Large darkly staining discrete nodules separated by pinkish foci occupied by histiocytes. Nodules are crowded and moulded against one another

Typical L & H cell – folded lobated nuclear membranes. Nucleoli are not prominent



Classical Hodgkin lymphoma Lymphocyte rich HL

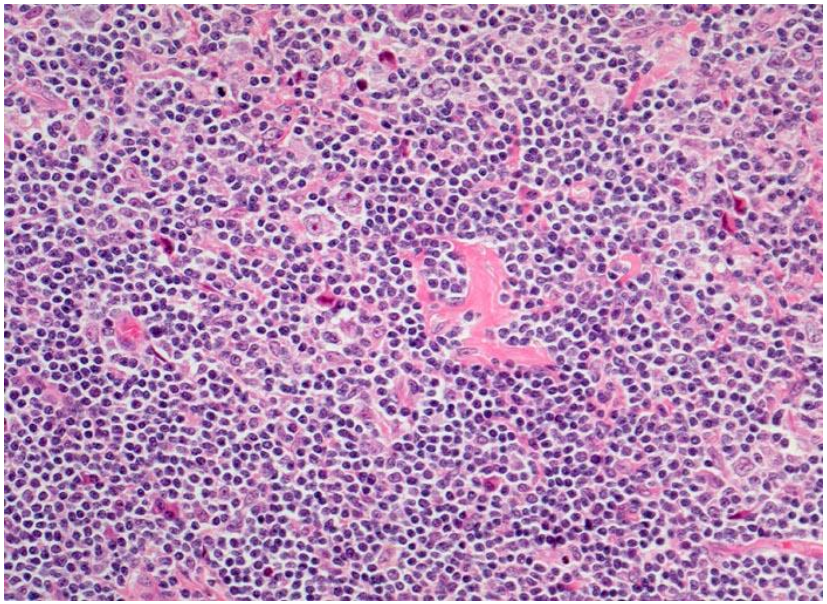
Incidence – Approx 5%

Slightly older age (median – 43yrs)

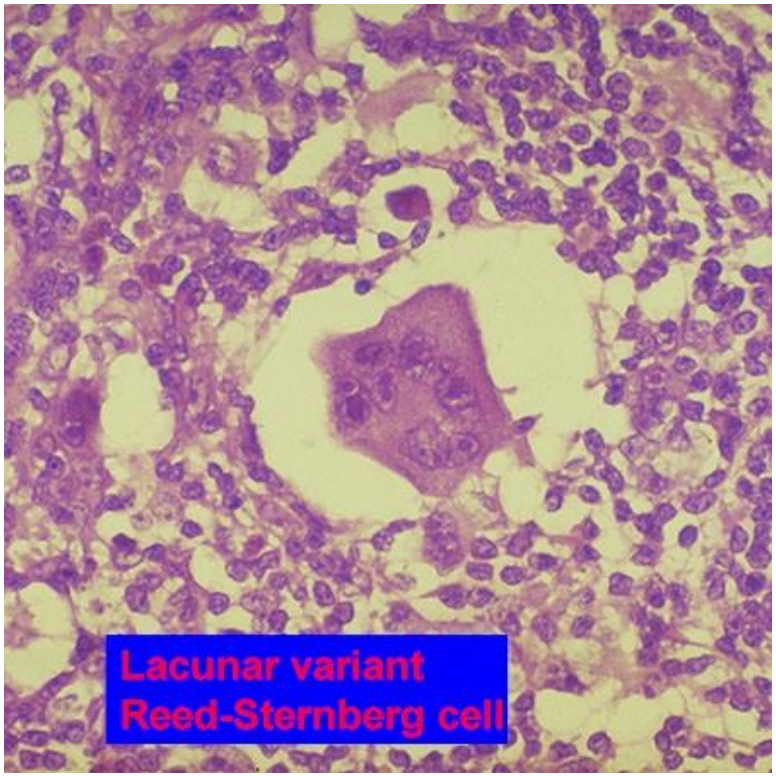
B symptoms rare

Microscopy :

- RS cells very few / absent



Nodular sclerosing HL



Commonest – 60%

Predominantly in females.

Mediastinal lymph nodes involved.

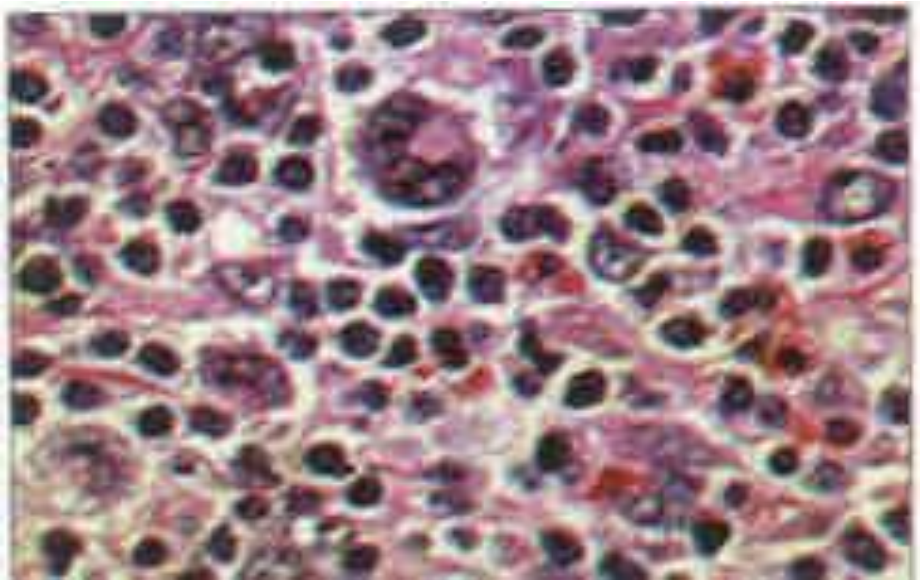
Nodularity of the architecture with lacunar cells.

Mixed cellular HL

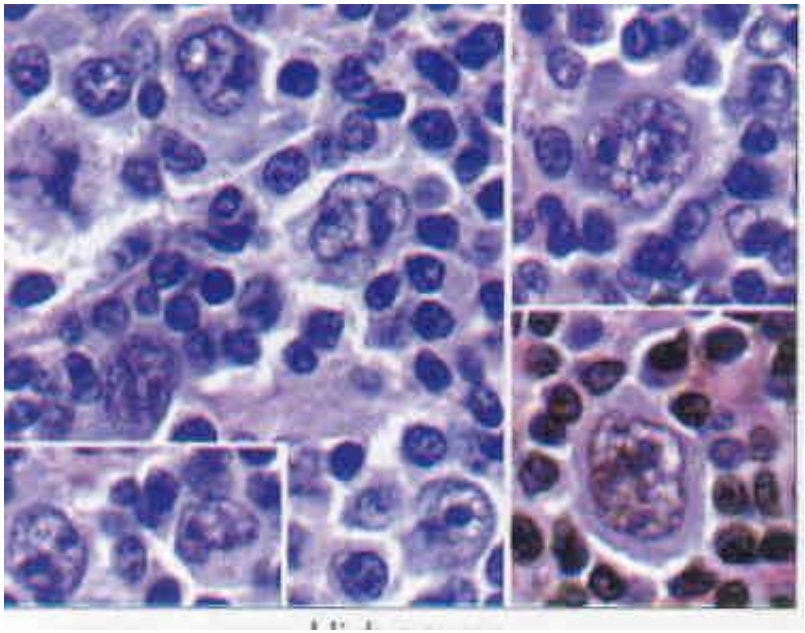
Any age

Numerous RS cells present. (easy to find)

Mixed cellularity of the background non neoplastic cells.



Lymphocyte depleted HL



Poor prognosis

Mainly in elderly

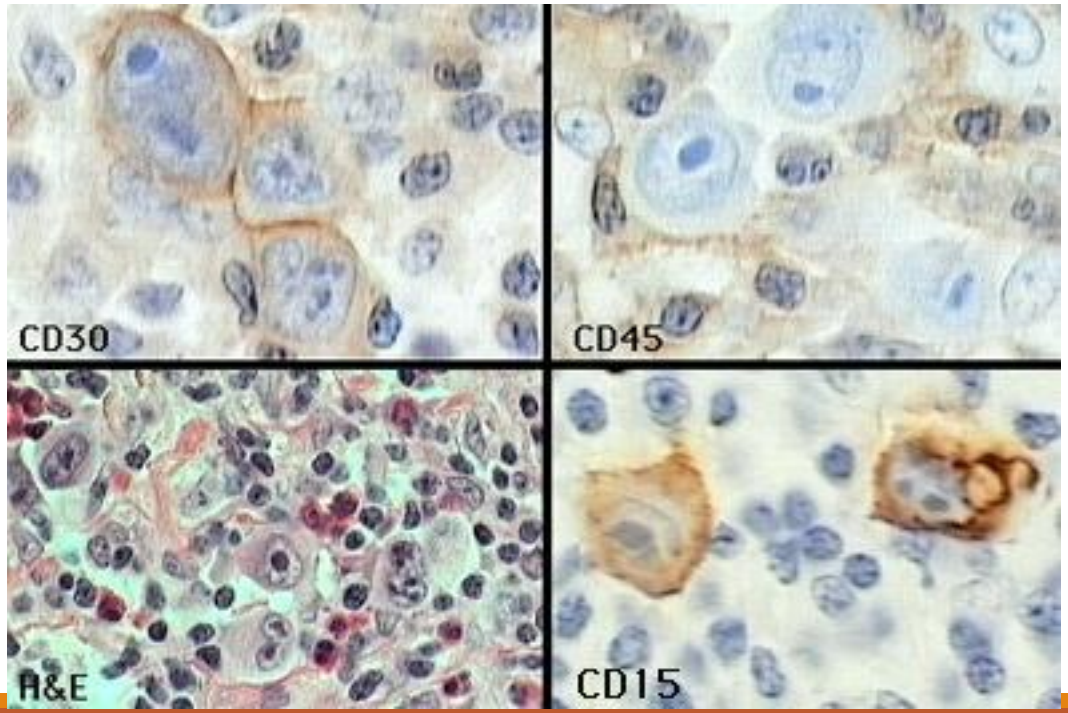
Numerous RS cells and mononuclear RS cells or Hodgkins cells.

Ancillary studies

Distinguish HL from

- Immunoblast reactions
- Unusual variants of NHL

CD15 and CD30 antigens in golgi and on cell membrane of R-S cells most useful

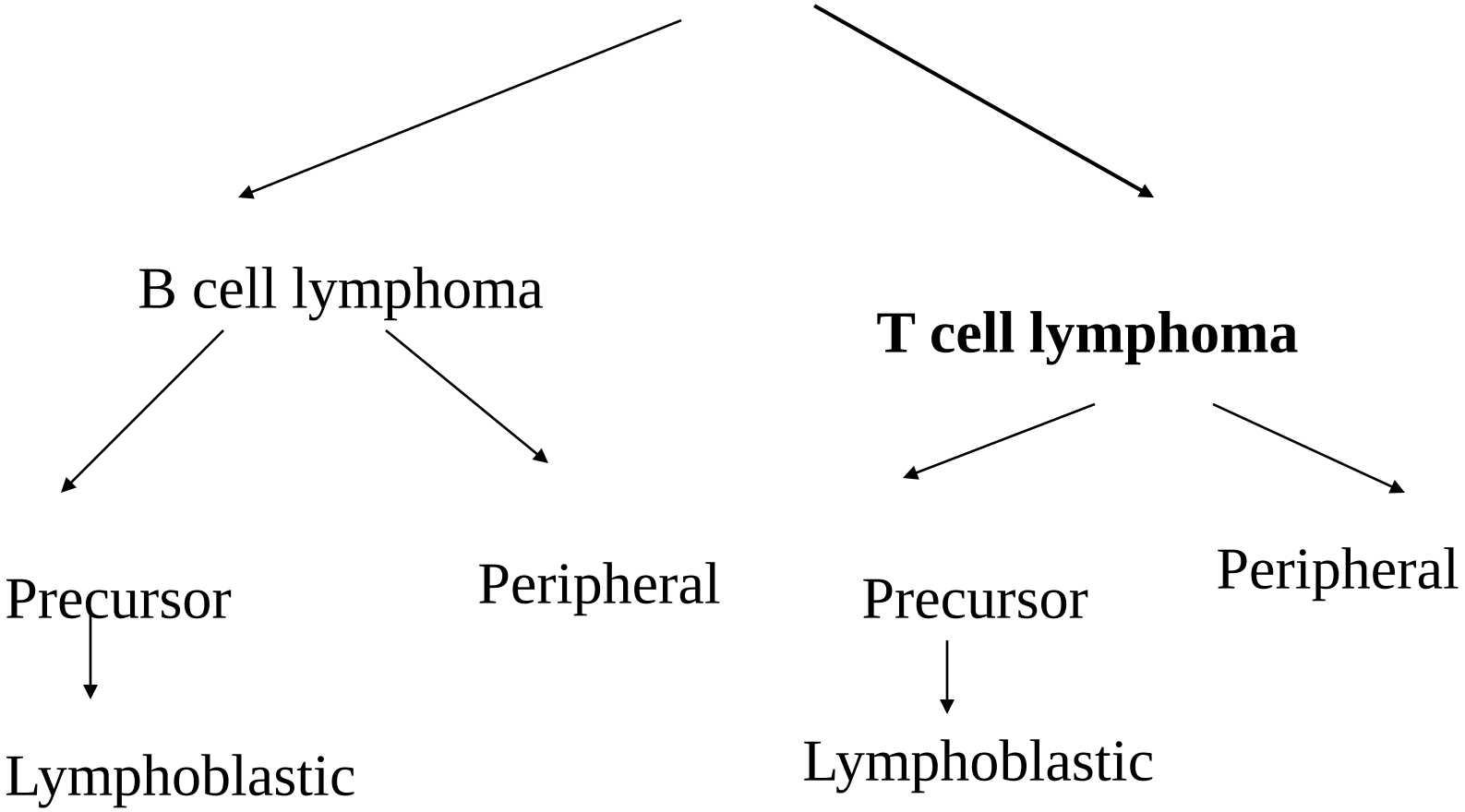


Non - Hodgkins lymphoma (NHL)

Different types of classifications.

- Working formulation
- Kiel classification
- Lukes & Collins classification
- REAL classification
- **WHO - REAL classification**.

Non Hodgkins lymphoma. (WHO -REAL classification)



B-Cell Neoplasms	T/NK-Cell Neoplasms	Hodgkin's Lymphoma
•Precursor B-cell lymphoblastic leukemia/lymphoma	•Precursor T cell lymphoblastic leukemia/lymphoma	•Lymphocyte predominance, nodular
<u>Peripheral B-cell neoplasms</u>	<u>Peripheral T-cell and NK-cell neoplasms</u>	•Classical HL
•B-cell CLL/SLL	***Predominantly leukemic/disseminated***	•Lymphocyte rich classical HL
•B-cell prolymphocytic leukemia	•T-cell prolymphocytic leukemia	•Nodular sclerosis
•Lymphoplasmacytic lymphoma	•T-cell large granular lymphocytic (LGL) leukemia	•Mixed cellularity
•Mantle cell lymphoma	•NK cell leukemia	•Lymphocyte depletion
•Follicular lymphoma	•Adult T-cell leukemia/lymphoma	•Unclassifiable classical HL
•Extranodal marginal zone B-cell lymphoma, MALT type (+/- monocytoid B cells)	***Predominantly nodal***	
•Nodal marginal zone B-cell lymphoma (+/-monocytoid B cells)	•Angioimmunoblastic T-cell lymphoma	
•Splenic marginal zone B-cell lymphoma (+/-villous lymphocytes)	•Peripheral T-cell lymphoma unspecified	
•Hairy cell leukemia	•Anaplastic large cell lymphoma, T/null-cell	
•Diffuse large B-cell lymphoma	***Predominantly extranodal***	
•Burkitt lymphoma	•Mycosis fungoides	
•Plasma cell myeloma	•Sezary syndrome	
•Plasmacytoma	•Primary cutaneous (CD30+ T-cell lymphoproliferative disorders)	
	•Subcutaneous panniculitis-like T-cell lymphoma	
	•NK/T cell lymphoma, nasal and nasal-type	
	•Enteropathy-type intestinal T-cell lymphoma	
	•Hepatosplenic T-cell lymphoma	
	g/d (gamma/delta)	
	a/b (alpha/beta)	

Indolent versus aggressive

Indolent

- Small lymphocytic lymphoma/CLL
- Follicular lymphoma, Grades 1/2
- Extranodal Marginal zone lymphoma of MALT type
- Nodal marginal zone lymphoma
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Lymphoplasmacytic lymphoma
- Plasma cell myeloma
- Plasmacytoma

- Cutaneous T cell lymphoma
- Cutaneous CD30+ anaplastic large cell lymphoma

Aggressive

- Prolymphocytic leukemia
- Large B cell lymphoma
- Burkitt lymphoma
- Mantle cell lymphoma

- Anaplastic large cell lymphoma
- All peripheral T cell lymphomas

Divides B and T

Indolent lymphomas

Diseases of slow accumulation, due to defective apoptosis

Often widespread at diagnosis

Prolonged natural history, median survivals >5 years

Will usually respond to chemo- or radiation therapy

Will usually relapse, but respond to same or alternative tx

Currently **incurable** unless

- Localized disease or
- Marrow ablation with some type of stem cell transplant

Classification of indolent lymphomas- later

Aggressive lymphomas

Lymphomas frozen at stages characterized by replication and accelerated growth

Diseases of defective cell cycle control

More often localized at presentation than indolent lymphomas

More often extranodal

Shorter natural history; median survival </= 2 years

Require more aggressive therapy to achieve "clinical remission"- disappearance of all detectable disease

Despite short natural history, curable disease in some with aggressive therapy

- Approximately 30-40% of adults
- 50-80% children

All childhood lymphomas of this type

Classification of lymphomas

Subtyping or **classification** within the two groupings necessary, because different subtypes have

- Distinct clinical presentations
- Can require different therapy
- Have differing prognoses, reflecting different mechanisms of molecular pathogenesis.

Unfortunately, rarely unanimous acceptance of any one classification scheme.

Intermittent upgrading of classification, with new terminology, reflecting new information and classifier bias

Classification often lags behind advances in immunology, research pathology

B cell lymphoma

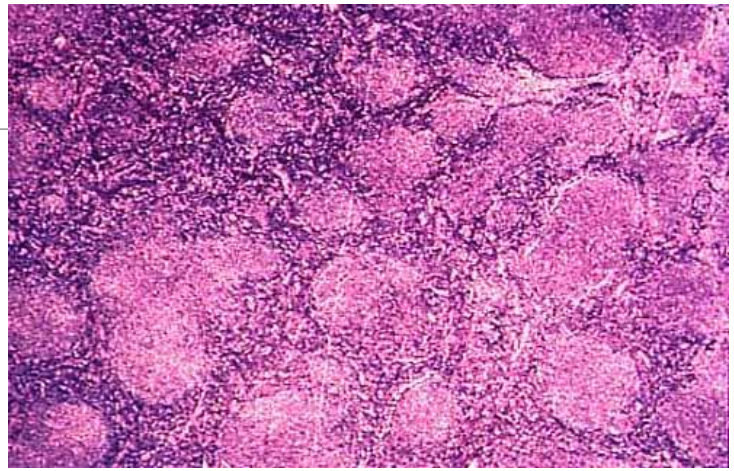
Peripheral

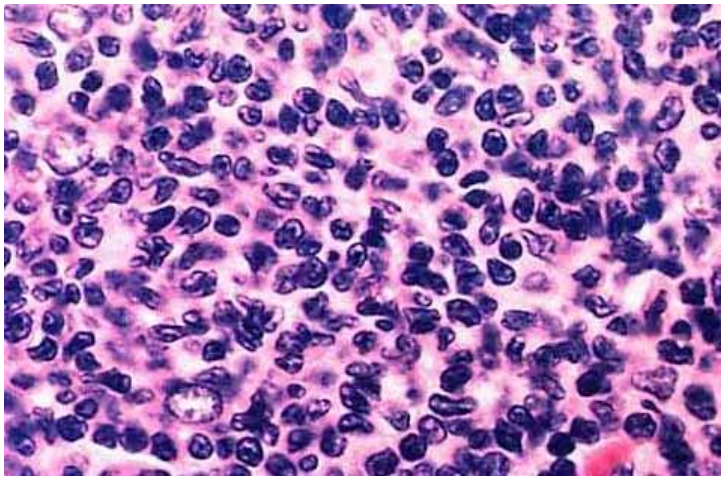
- B CLL / SLL
- B prolymphocytic lymphoma
- Mantle cell lymphoma
- Follicular lymphoma
- Extranodal & nodal & splenic marginal zone B cell lymphoma (Maltoma)
- Hairy cell leukaemia
- Diffuse large cell B cell lymphoma
- Burkitt’s lymphoma
- Plasmactyoma / plasma cell myeloma

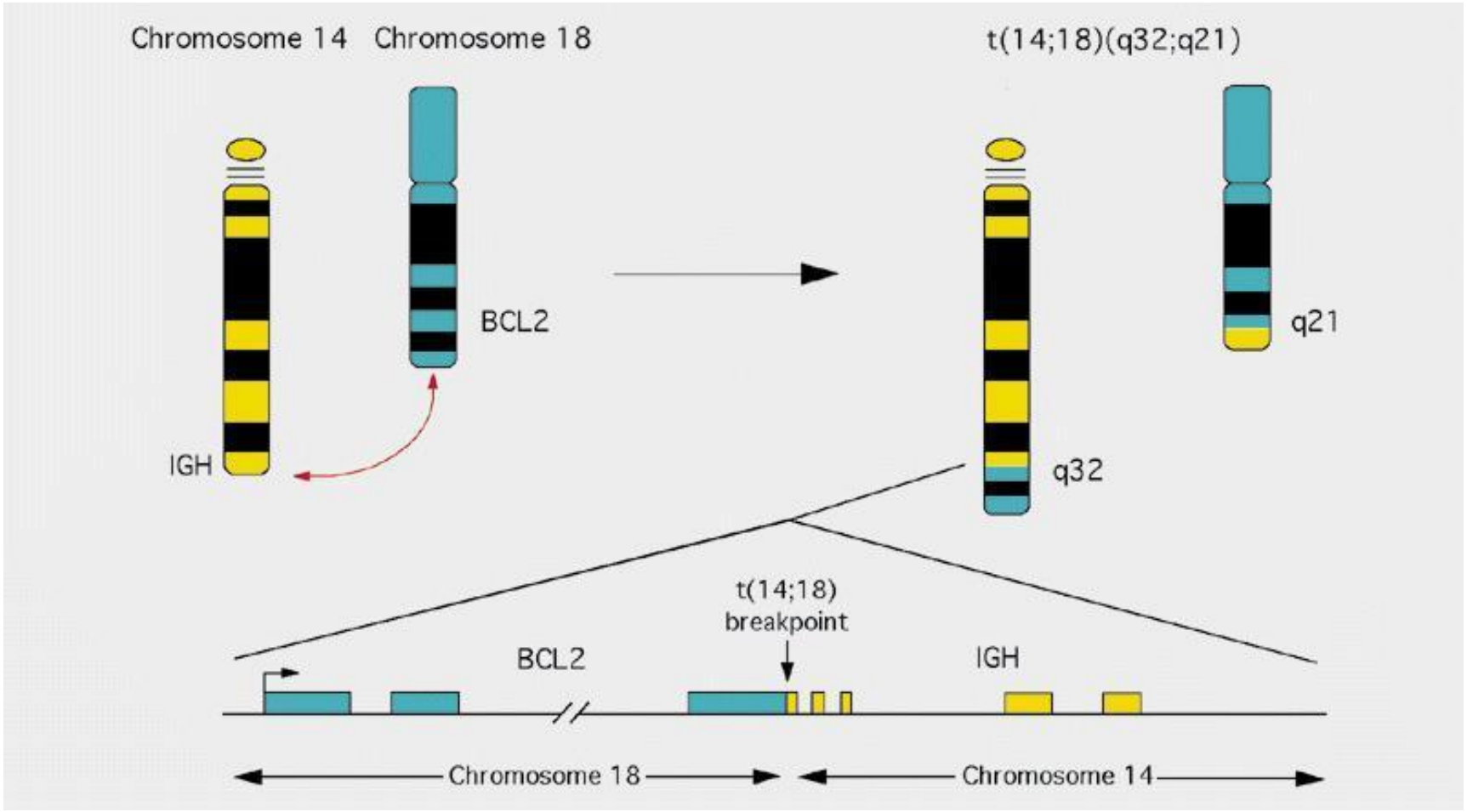
Follicular lymphoma Grade I

Pathology/diagnosis

- Benign equivalent: small cleaved cell of germinal center
- Clumped chromatin and infrequent nucleolus like small lymphocyte
- Irregular nuclear profile, with nuclear folds or "cleavages"
- Retain follicular structure, but monotonous accumulation of single cell type

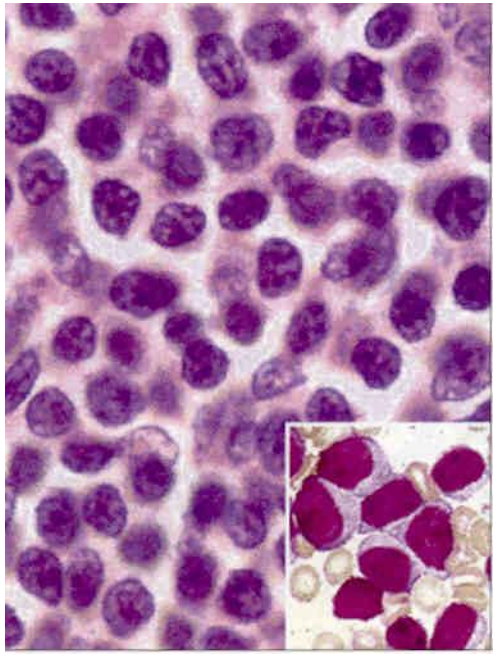




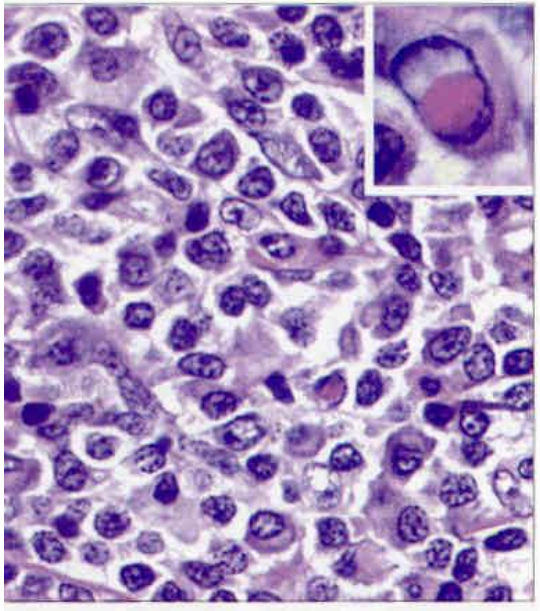

Chromosome 14
Chromosome 18
t(14;18)(q32;q21)
BCL2
IGH
q21
q32
t(14;18)
breakpoint
BCL2
IGH
Chromosome 18
Chromosome 14

Small cell lymphoma – low grade

B cell lymphoma - CLL

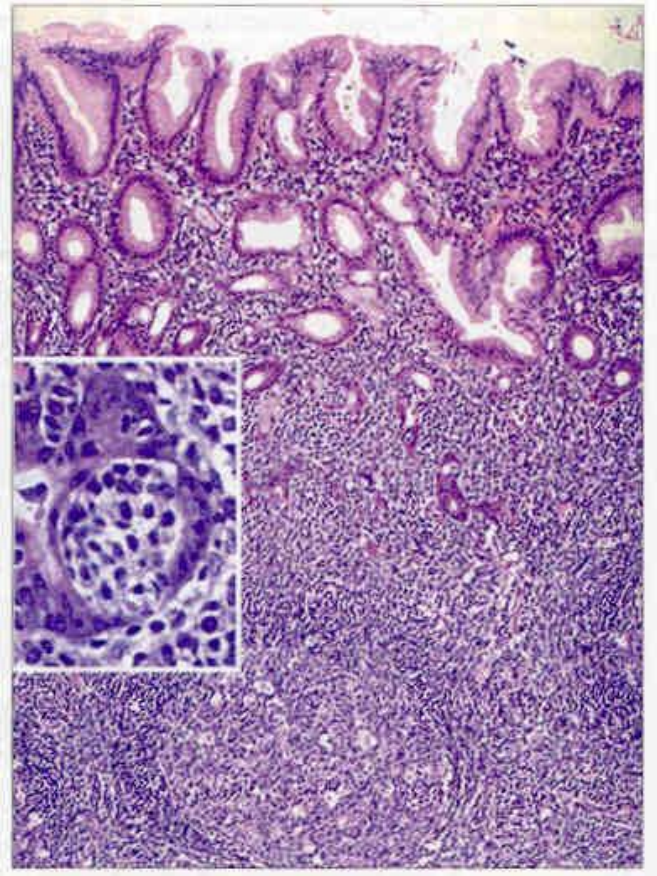


Plasmacytoid lymphoma



Marginal zone lymphoma - Maltoma

Lymphoepithelial lesions



Examples: aggressive B cell lymphoma- Diffuse large B cell lymphoma

Clinical

- Most common lymphoma- 30% NHL
- Disease of adults and children, but median age 64
- Limited versus widespread disease ~1:1
- Presents with rapidly enlarging masses
- Approximately 40% curable with aggressive chemotherapy/ stem cell transplant
  - Partially predictable by International Prognostic Index (later)

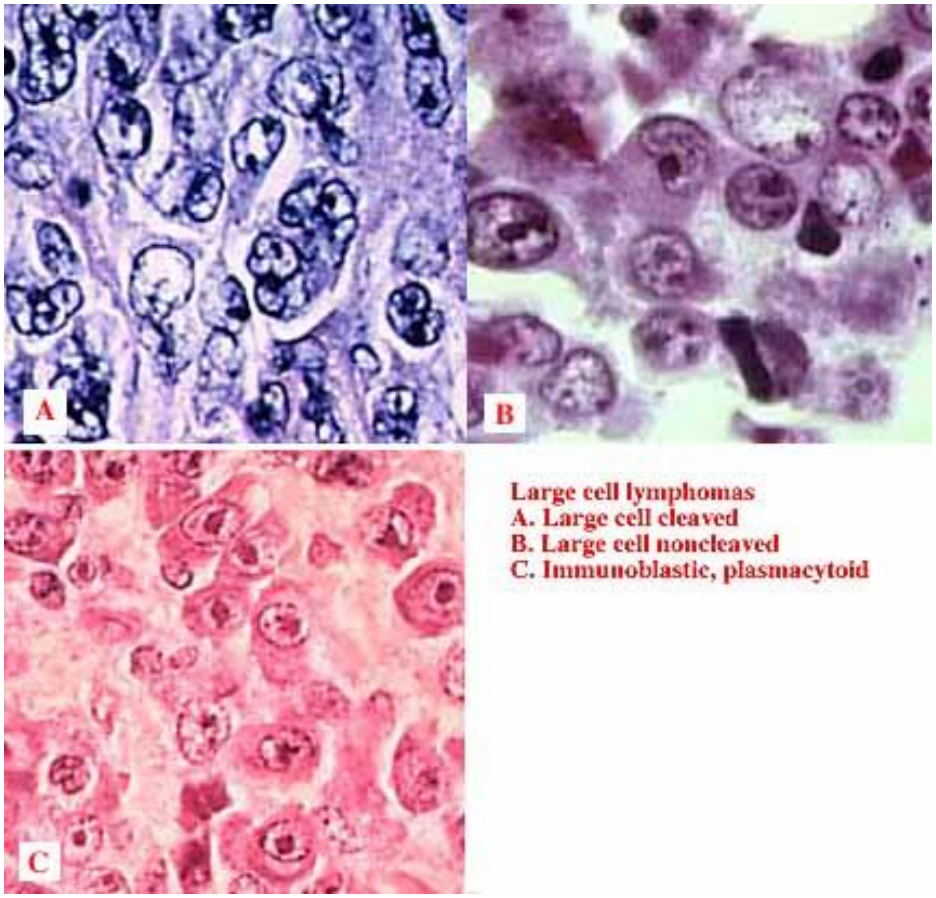
Pathogenesis

- Not as clearly defined - several cytogenetic abnormalities associated with large cell lymphoma, but no defining one

Diffuse Large B cell lymphoma

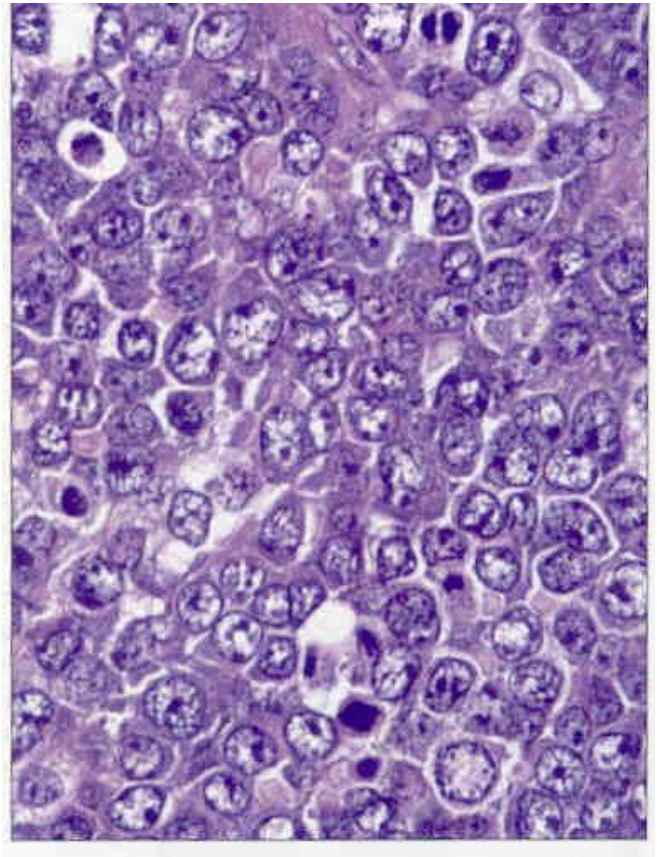
Pathology

- Benign equivalent- large replicating B cells of germinal center and paracortex
- Diffuse infiltration of lymph node
- Often necrosis; increased mitotic rate
- Cytology: Oval or cleaved nucleus with vesicular chromatin and 1-3 nucleolus
- Nucleus larger than that of reactive macrophage
- Several cytologic subtypes initially felt to have differing clinical behavior.
- Yielded division into intermediate versus high grade types- now not felt valid or significant without immunologic/molecular evidence
- Immunophenotype characterized by monoclonal light chain, CD19 expression,with variable expression of other B cell associated antigens



Large cell lymphomas
A. Large cell cleaved
B. Large cell noncleaved
C. Immunoblastic, plasmacytoid

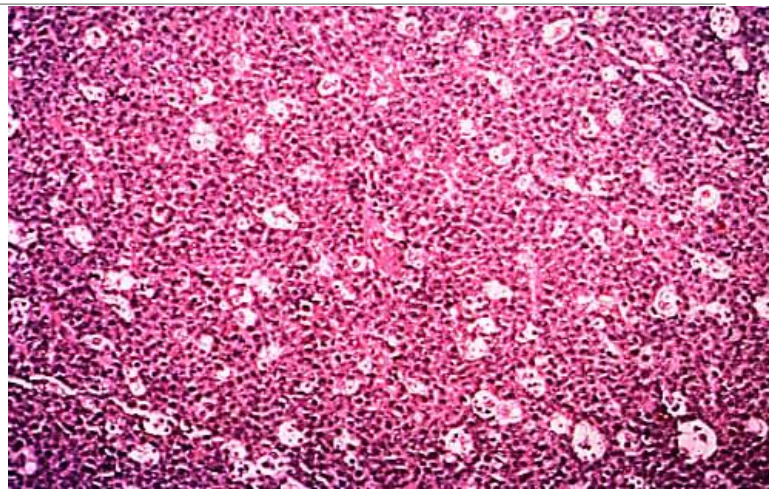
B cell - Large cell lymphoma

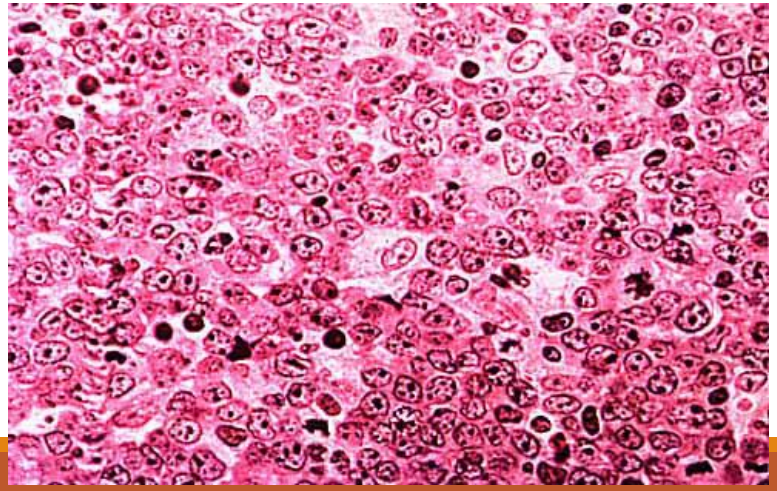


Burkitt's lymphoma

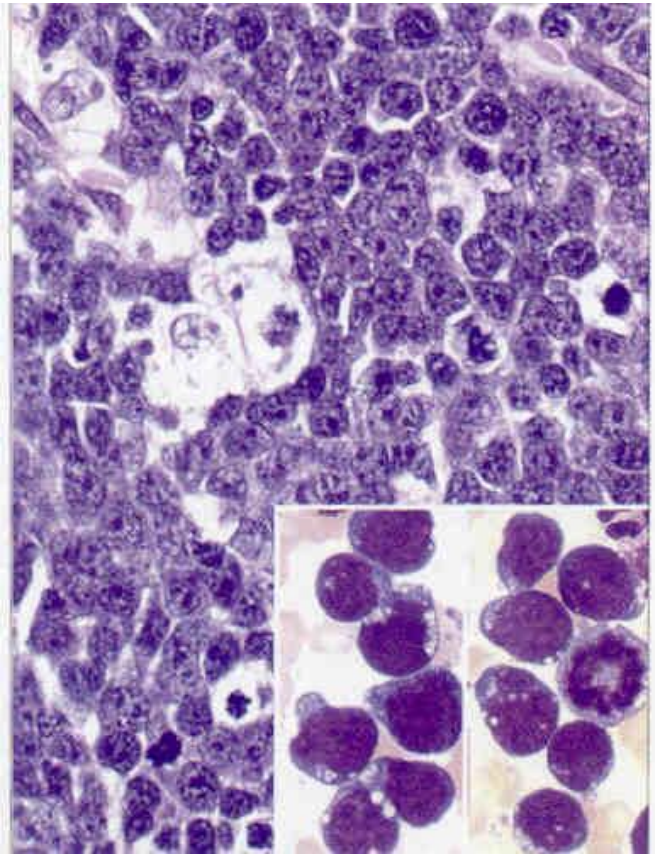
Pathology

- Benign equivalent is the replicating small noncleaved cell of germinal center:
- Diffuse infiltration of lymph node
- Very high mitotic rate, lot of ineffective proliferation;
- Attracts macrophages to phagocytose leading to starry sky pattern at low power
- Cytology: round nucleus, smaller than that of reactive macrophage
- Vesicular chromatin and 2-5 nucleoli





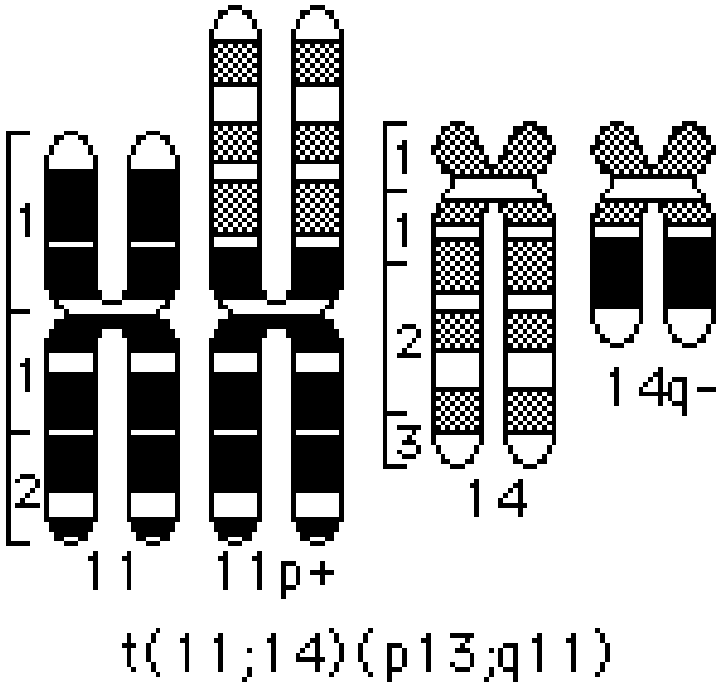
B cell Burkitts lymphoma



Mantle cell lymphoma

Clinical

- 6% of lymphomas
- Disease of adults (median age 63)
- Usually widely disseminated
- Poor response to all attempted therapies,
- ? curable with transplant
- 5yr survival 27%



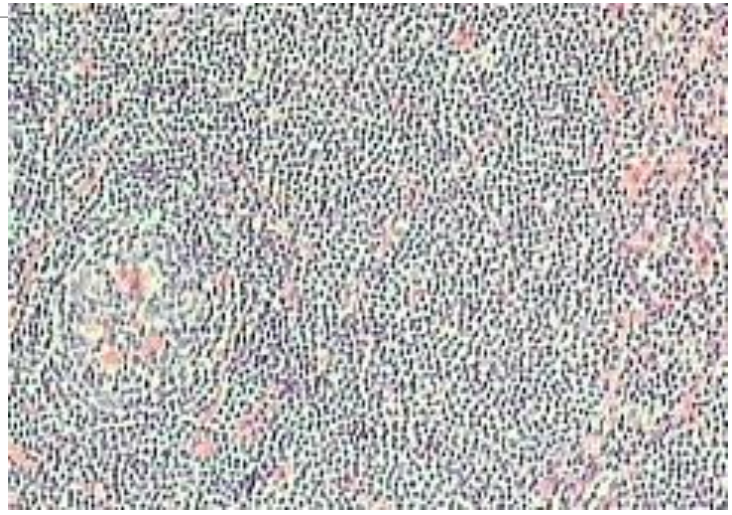
Pathogenesis

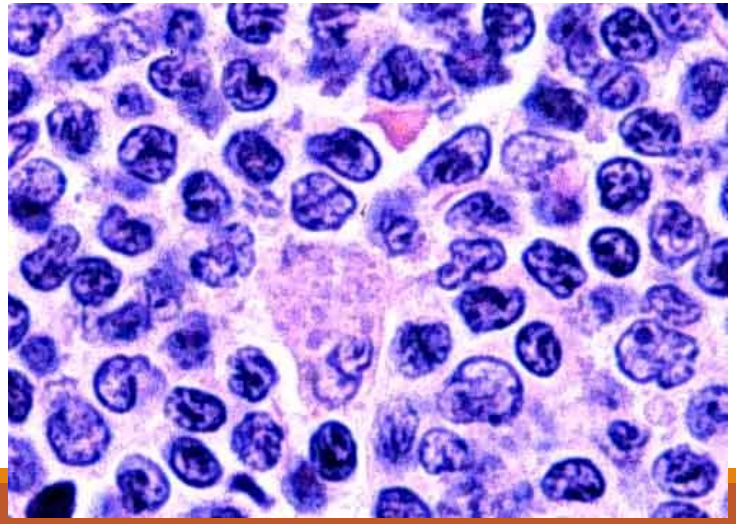
- Due to t(11;14)
- Upregulates Bcl1 (cyclin D1), a cell cycle regulator

Mantle cell lymphoma

Pathology/Diagnosis

- Benign equivalent is lymphocyte of inner mantle zone
- Cytology similar to cleaved cell, but nuclear irregularities not as prominent
- Nodal infiltration diffuse, vaguely nodular or "mantle zone" around residual benign follicles
- Large cell progression infrequent
- Immunophenotype:
  - Positive: monoclonal light chain, CD19, CD5, Bcl1 (and Bcl2)
  - Negative CD10, CD23





T cell lymphomas-Precursor T

Clinical

- Disease of teenagers; boys>girls
- Can present as acute leukemia or mediastinal mass+/- marrow involvement
- Aggressive lymphoma/leukemia, but curable: ~70% with appropriate multiagent chemotherapy

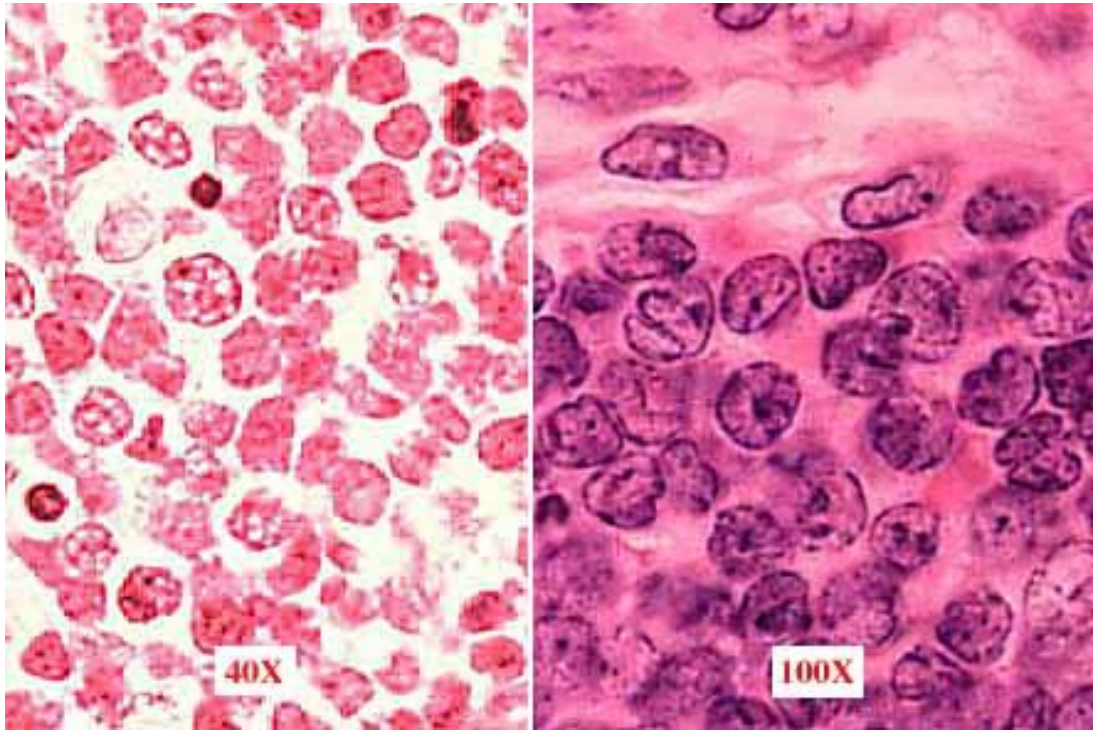
Pathogenesis

- No single gene culprit, but frequently involve translocation of (onco)genes to site of T cell receptor genes, --> upregulation of proteins

T cell lymphomas-Precursor T

Pathology

- Benign equivalent immature T cells of thymus
- Histology: Diffuse infiltration of thymus/adjacent lymph nodes
- Cytology: “Blast cells” of intermediate size with oval to “convoluted” nuclear profiles, fine chromatin and 0-1 nucleolus
- Again need immunology to distinguish from pre-B



Peripheral T cell lymphomas

Predominantly leukemic/disseminated

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic (LGL) leukemia
- NK cell leukemia
- Adult T-cell leukemia/lymphoma

Predominantly nodal

- Angioimmunoblastic T-cell lymphoma
- Peripheral T-cell lymphoma unspecified
- Anaplastic large cell lymphoma, T/null-cell

Predominantly extranodal

- Mycosis fungoides
- Sezary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
- Subcutaneous panniculitis-like T-cell lymphoma
- NK/T cell lymphoma, nasal and nasal-type
- Enteropathy-type intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma

Key points regarding T cell lymphomas

Clinical

- Represent 20% all lymphomas
- More often extranodal than B
  - Can involve skin, midline facial area, liver
  - Very characteristic clinical presentations
- Most diseases bad: high stage, and poorer response to therapy than B cell lymphomas of all grades

Pathogenesis:

- Characteristic cytogenetic findings associated with several types
  - Anaplastic large cell lymphoma- t(2;5): ALK1 gene
  - Hepatosplenic T cell lymphoma- Isochromosome 7

Key points regarding T cell lymphomas

Pathology

- Cytologic features not as predictive of behavior as B cell lymphomas
  - Anaplastic large cell lymphoma --> better prognosis than most indolent B cell lymphomas- 77% 5 year survival
  - Mycosis fungoides, indolent cutaneous lymphoma, incurable, but with long clinical course
- Immunophenotypic studies frequently demonstrate
  - Loss of normal T cell associated antigens
  - Antigens associated with Natural Killer cell function
  - Immunohistochemistry absolutely necessary to recognize

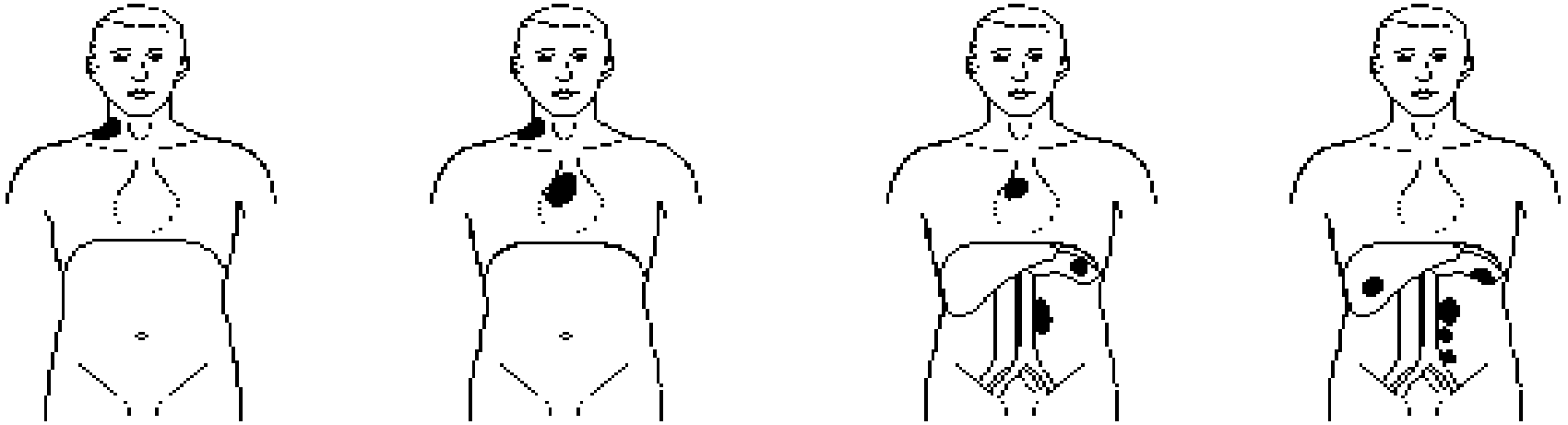
Clinical staging of lymphomas

Defines extent of disease; determines therapy and prognosis

Based on physical, radiologic examination, bone marrow biopsy and aspiration

Ann Arbor Staging system

B symptoms- fever, weight loss > 10% body weight, night sweats



Stage subdivision: A-asymptomatic B-unexplained weight loss>10% in 6m and/or fever and/or night sweats

Extralymphatic = tissue other than lymph nodes, thymus, spleen, Waldeyer's ring, appendix & Peyer's patches

Staging – Ann Arbour classification

TABLE 14–14. CLINICAL STAGING OF LYMPHOMAS

Stage	Description	Five-Year Survival (%)
I	Single lymph node group or contiguous lymph node on same side of diaphragm	90
II	Two or more lymph node groups or lymphatic tissues on same side of diaphragm	70
III	Involvement of lymphatic tissue on both sides of diaphragm	40
IV	Involvement of extranodal sites, e.g., bone marrow, liver, lung, skin	20

International Prognostic Index 1

- Clinical features identifying prognostic subsets of diffuse large cell lymphoma
- Identified through retrospective statistical analysis of large set patients
- Assigned 1 point for each bad feature

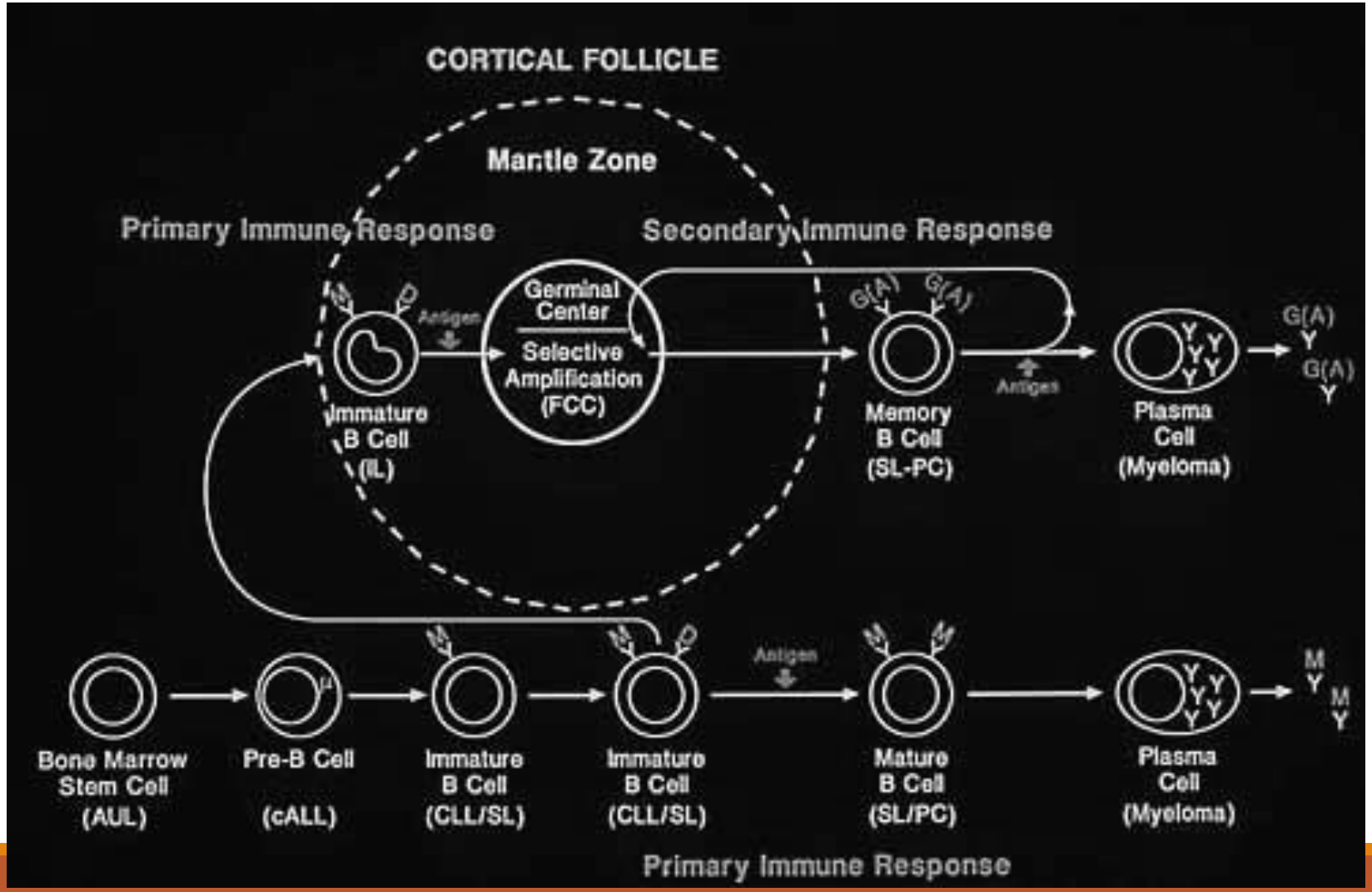
Table 3. Factors Independently Prognostic of Overall Survival in the Training Sample.

Factor	Relative Risk	P Value
All patients (n = 1385)		
Age (≤60 vs. >60)	1.96	<0.001
Serum LDH (≤1× normal vs. >1× normal)	1.85	<0.001
Performance status (0 or 1 vs. 2–4)	1.80	<0.001
Stage (I or II vs. III or IV)	1.47	<0.001
Extranodal involvement (≤1 site vs. >1 site)*	1.48	<0.001
Patients ≤60 years old (n = 885)		
Stage (I or II vs. III or IV)	2.17	<0.001
Serum LDH (≤1× normal vs. >1× normal)	1.95	<0.001
Performance status (0 or 1 vs. 2–4)	1.81	<0.001

*This was the only factor that did not retain independent prognostic significance in patients ≤60 years old (≤1 site vs. >1 site: relative risk, 1.20; P = 0.134).

Peripheral B-cell lymphomas

- **Lymphomas frozen at various stages of *antigen dependent* B cell maturation and differentiation**



CD markers in the diagnosis

LCA – Leukocyte common antigen

CD20 – B cell marker

CD3 – T cell marker

CD 138 – plasma cell marker

CD 68 – histiocytic marker