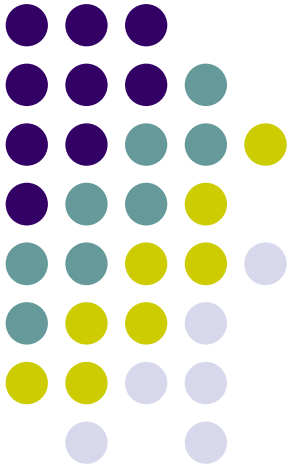
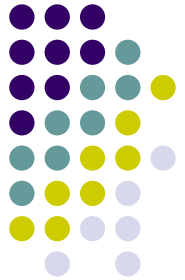
Hodgkin's Lymphoma

Dr. Geetika Vohra
Department of Pathology



LYMPH NODE

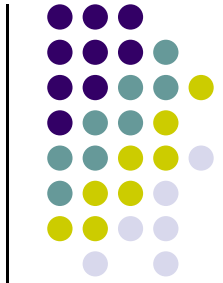


- Imp component of lympho reticular system
- Others- thymus
- spleen
- tonsils inc adenoids
- Peyer s patches
- Less organised –Bone Marrow
- MALT-lungs , GIT

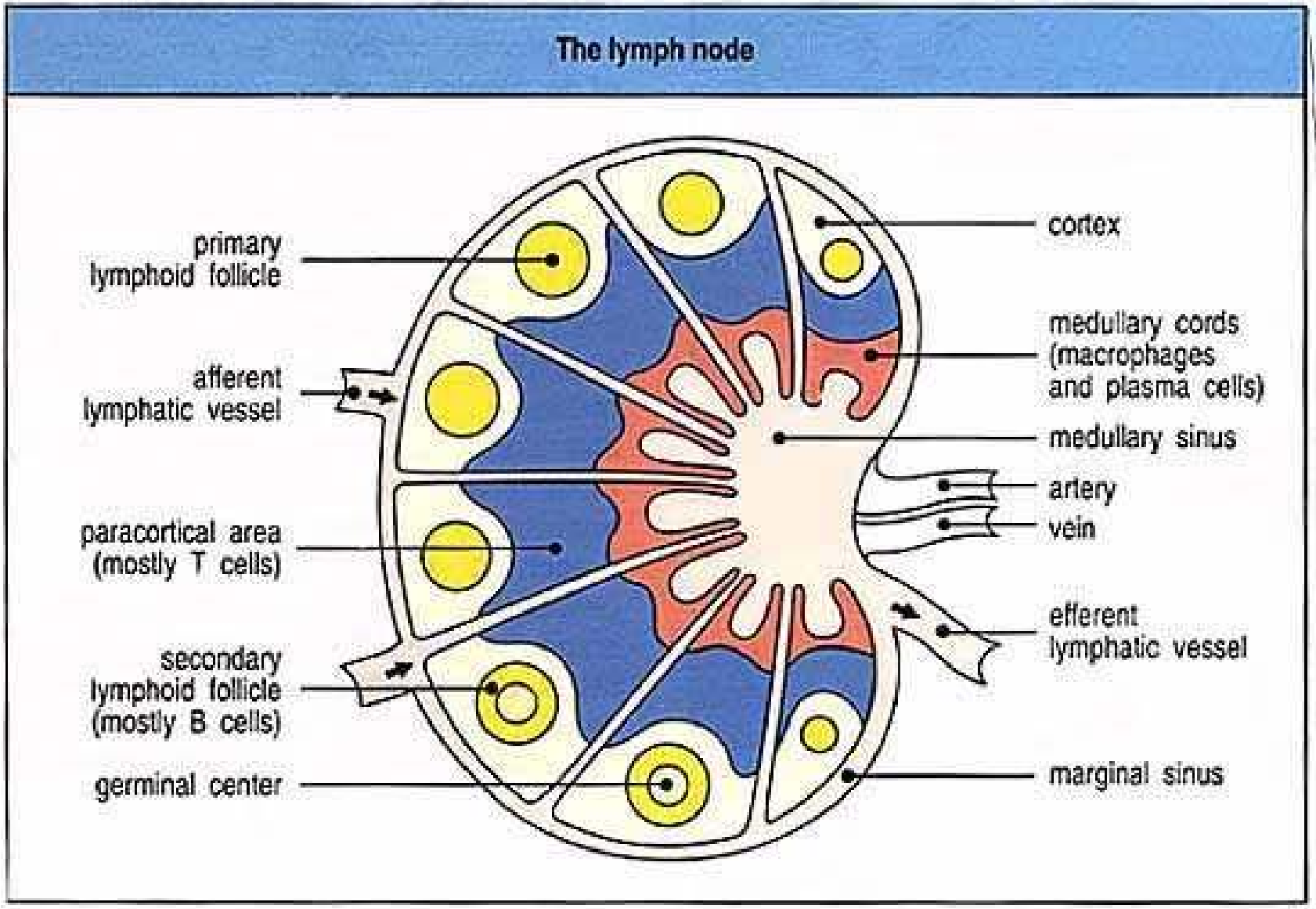
Structure of LN

- Capsule-perforated by afferent lymphatic channels
- Enter into sub capsular sinus
- Branch
- Terminate at concavity or hilum as efferent lymphatic vessel

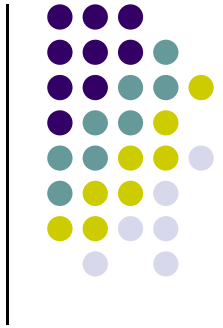
Lymphoid folls



- B cell areas
- Ag.ic stim –dev G. C.
- Composed of FCC
- Surr by small LCs(mantle zone)
- Outside mantle zone –marginal zone.


The lymph node
primary lymphoid follicle
afferent lymphatic vessel
paracortical area (mostly T cells)
secondary lymphoid follicle (mostly B cells)
germinal center
cortex
medullary cords (macrophages and plasma cells)
medullary sinus
artery
vein
efferent lymphatic vessel
marginal sinus

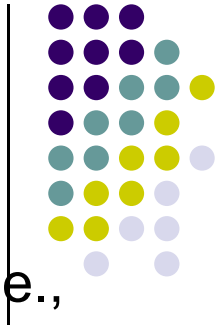
Causes of LN opathy



- Non neoplastic & neoplastic

- Non Neo-Inflammatory
- Immune response
- Neoplastic –primary
- Secondary(Metastatic deposits)
- Primary Lymphoma
- Plasma cell disorders
- Langerhans cell histiocytosis

Introduction



- Lymphomas are malignant tumours of lymphoreticular origin i.e., lymphocytes, histiocytes and their precursor cells.

- Usually lymphoma begins in and involves L. nodes predominantly, although other sites such as spleen, GIT, are frequent areas of origin as well.

- In advanced stage, infiltration of neoplastic cells are found in many organs throughout the body and several forms of lymphomas (SLL, lymphoblastic lymphoma, and Burkitt's lymphoma) have leukemic stages as part of their natural progression.

- Clinically and pathologically lymphomas are quite heterogeneous. However, two distinct clinico-pathologic groups are routinely distinguished: Hodgkin's lymphomas (HL) and non-Hodgkin's lymphomas (NHL).

Clinical Differences between HL & NHL

HL	NHL
More often localized to single axial group of nodes	More frequent involvement of multiple peripheral node
Orderly spread by contiguity	Non-contiguous spread
Extranodal involvement uncommon Rare involvement of mesenteric node, Waldeyer ring	Extranodal involvement common Common involvement of mesenteric node, Waldeyer ring

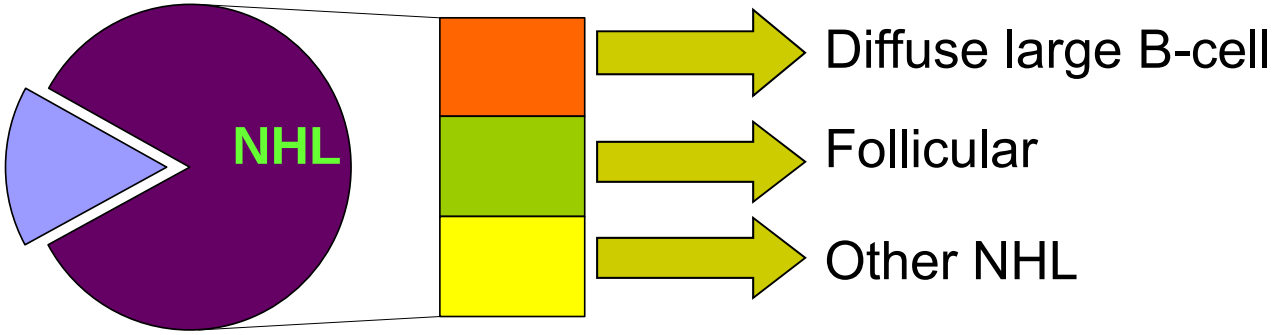
Epidemiology of lymphomas

- 5th most frequently diagnosed cancer in both sexes
- Males > females
- Incidence
  - NHL increasing
  - Hodgkin lymphoma stable

Relative frequencies of different lymphomas

Non-Hodgkin Lymphomas

Hodgkin lymphoma



~85% of NHL are B-lineage

Hodgkin's Lymphoma

- Originally described by Thomas Hodgkin in 1832
- Malignant lymphoma in which **Reed Sternberg (R.S.)** cells are present in a characteristic background of reactive inflammatory cells of various types accompanied by fibrosis of various degree.
- HL accounts for about 20-30% of lymphoma
- Overall Male>Female
- Incidence:
  - Bimodal peaks- one in young adult and second in 5^{th} decade

Etiopathogenesis of HL

- EBV- has been implicated in pathogenesis in HL on basis of epidemiological, serological studies. Recently, molecular studies revealed genome of EBV in R.S. cells in most of the cases.

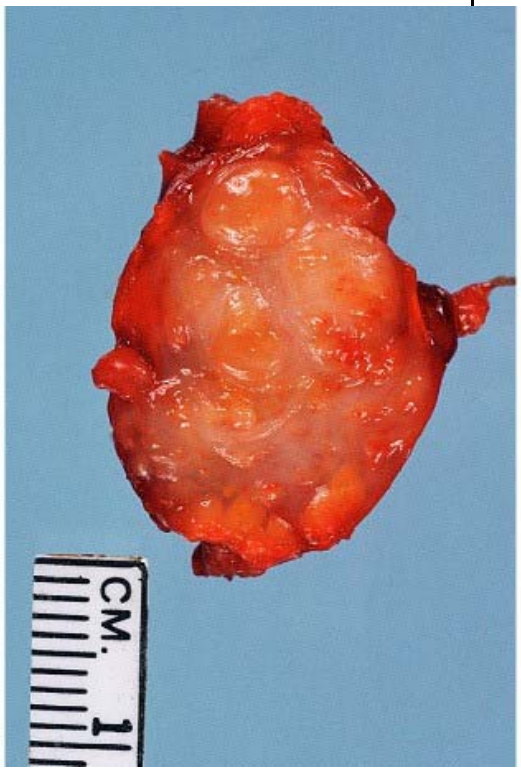
- Genetic etiology- HL is about 99 times more common in identical twin of affected case compared to general population.

- Cytokines- Presence of reactive inflammatory cells in HL is due to secretion of cytokines from R.S. cells

Hodgkin's Lymphoma

Gross Features:

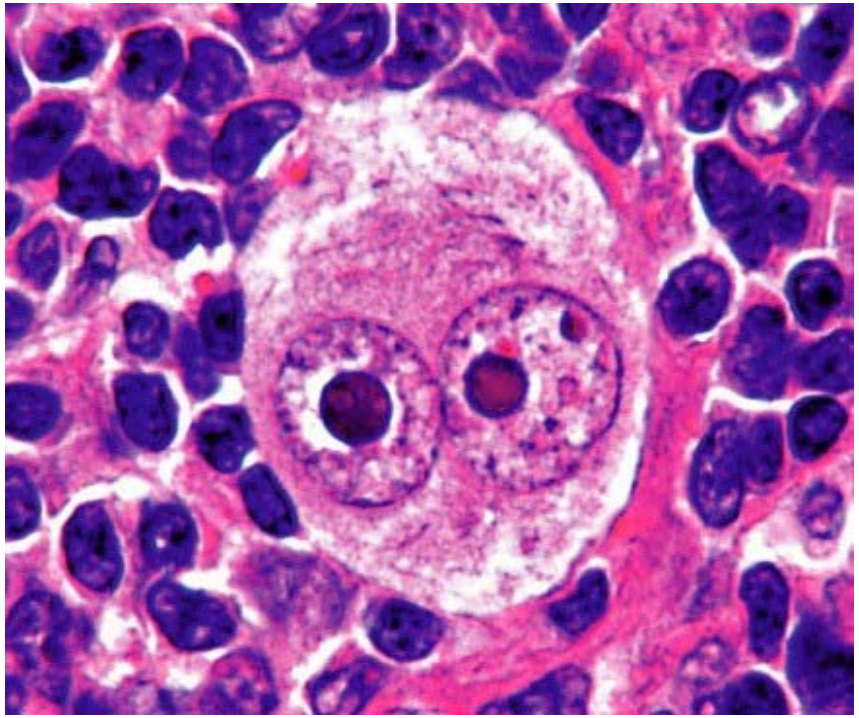
L. nodes are enlarged, soft to hard depending on the amount of fibrosis, foci of necrosis is present. In advanced stage several L. nodes from same group become matted together.

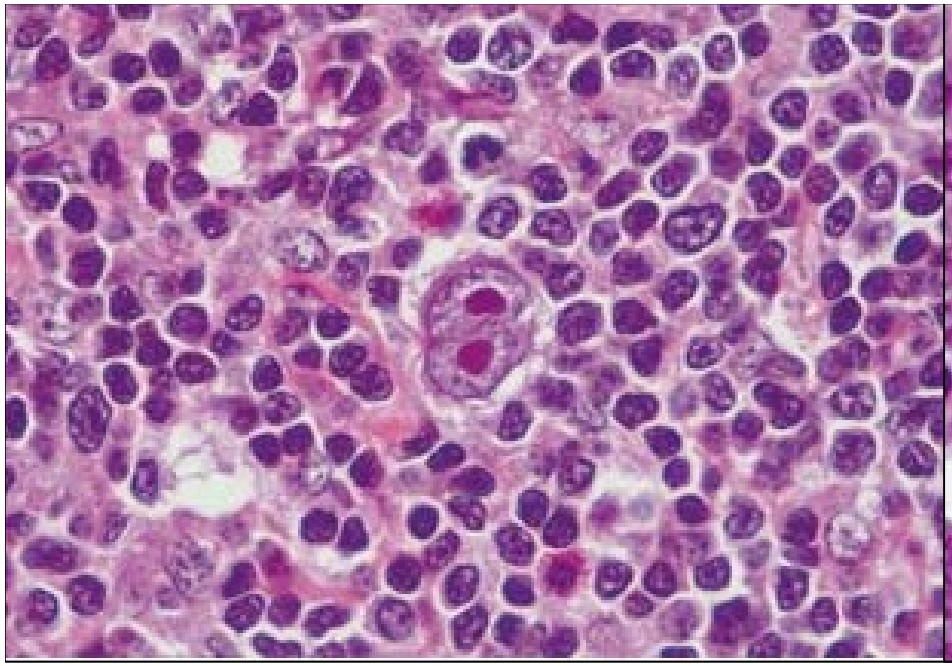


HL(gross): Note nodularity and sclerosis.

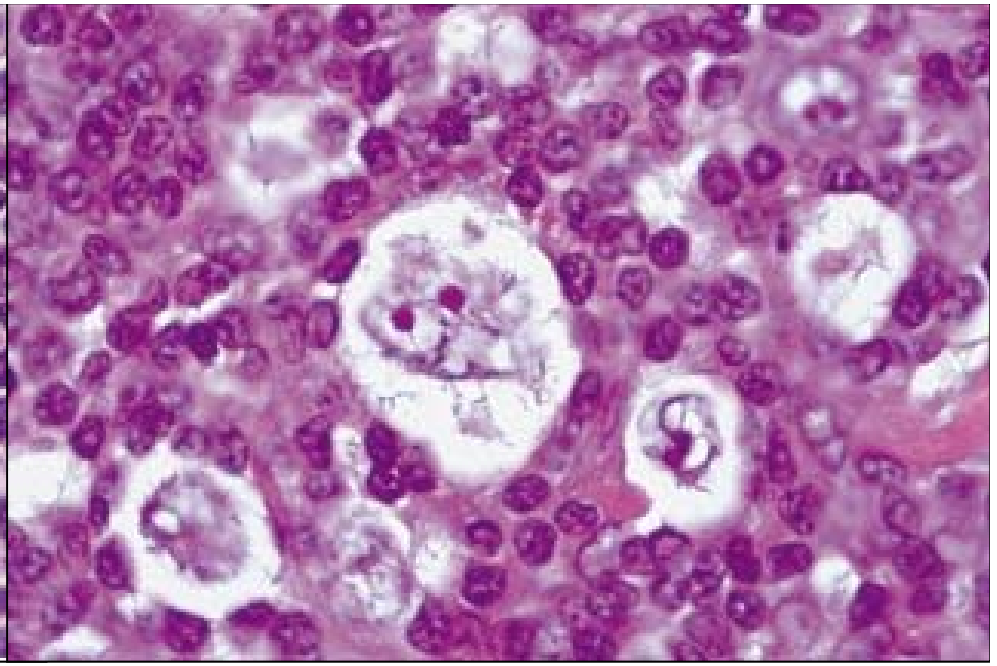
Hodgkin's Lymphoma

- **M/E:** R.S. cells are **large (20-50µm**) abundant weakly acidophilic cytoplasm witch may appear homogenous or granular **nucleus-bilobed or polylobed**, so that cell appear **binucleated or multinucleated**, nuclear membrane is thick and sharply defined. Nuclear pattern is vesicular, nucleolus is large rounded highly acidophillic centrally located surrounded by clear halo. In R.S. cells 2 nuclear lobes face each other **(mirror image) gives 'owl eye' appearance**, when nuclear lobation is lacking cells are k.a. mononuclear variants of R.S. cells/ Hodgkin's cells.



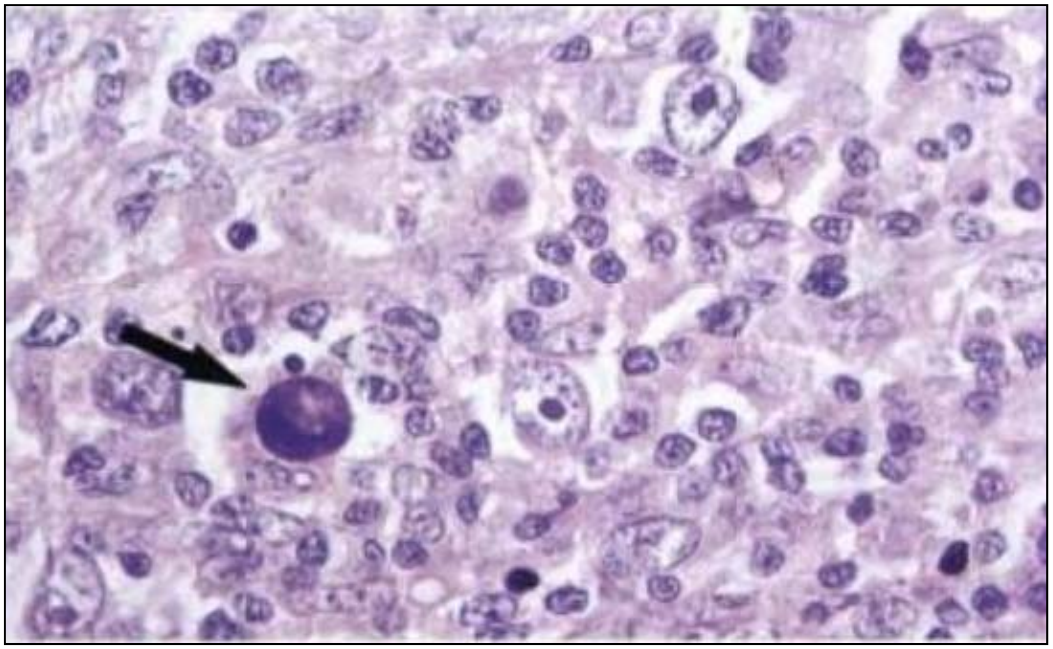


RS cell



Lacunar variant

Mummified variant



- Immunophenotype of HRS cells
- Positive markers

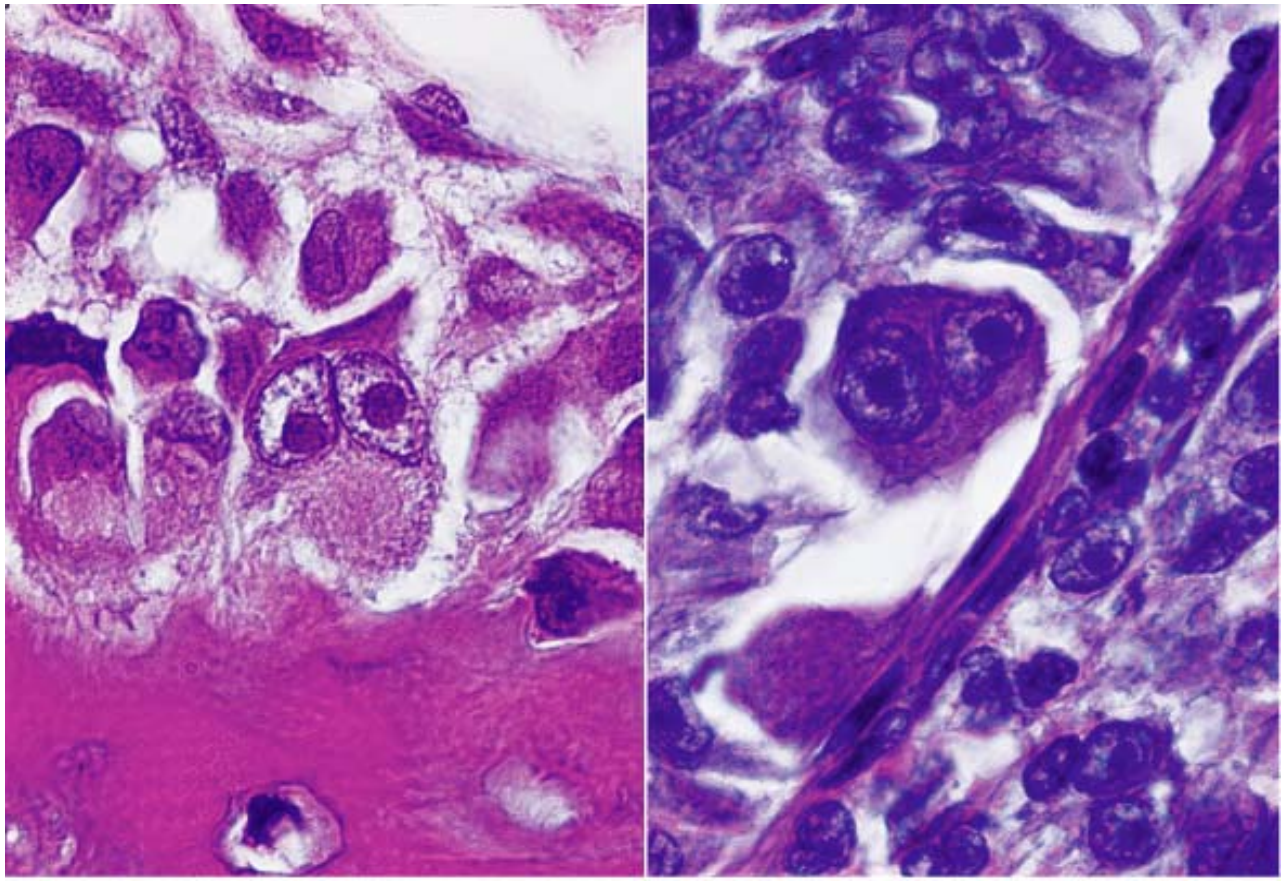
- **CD30 & CD15** (75-85%)- Membranous with accentuation in the Golgi region
- **PAX5**- 95%, weaker than reactive B-cells
- IRF/MUM1
- CD20- 30-40%
- CD79a- Less often expressed
- EBV infected cells- LMP1 and EBNA1

- Negative markers- EMA, OCT-2, BOB.1

- R.S. cells of HL needs to be differentiated from other mononucleated cells that may be present in L. nodes such as
  1. **Megakaryocytes-** but they are strongly PAS +ve, positivity for factor VIII.
  2. **Pleomorphic immunoblasts** seen in infectious mononucleosis, having basophillic nucleolus, irregular contour, seen in adjacent to nuclear membrane. Paranuclear hof- prominent , cytoplasm – amphophilic, surrounded mononuclear immunoblasts, plasmacytoid cells.
  3. **Neoplastic cells** from a variety of epithelial as well as mesenchymal tumour may resemble. E.g., Multiple myeloma, osteoblastoma,of bone, malignant lymphoma of NHL type may have cells like R.S. cells.
- So it is important to examine not only R.S. cells but also the background in which they are situated. The more cytologically atypical the lymphoid population less likely the diagnosis of Hodgkin's Lymphoma.

Reed–Sternberg-like cells in malignant melanoma (A), and osteoblastoma (B)

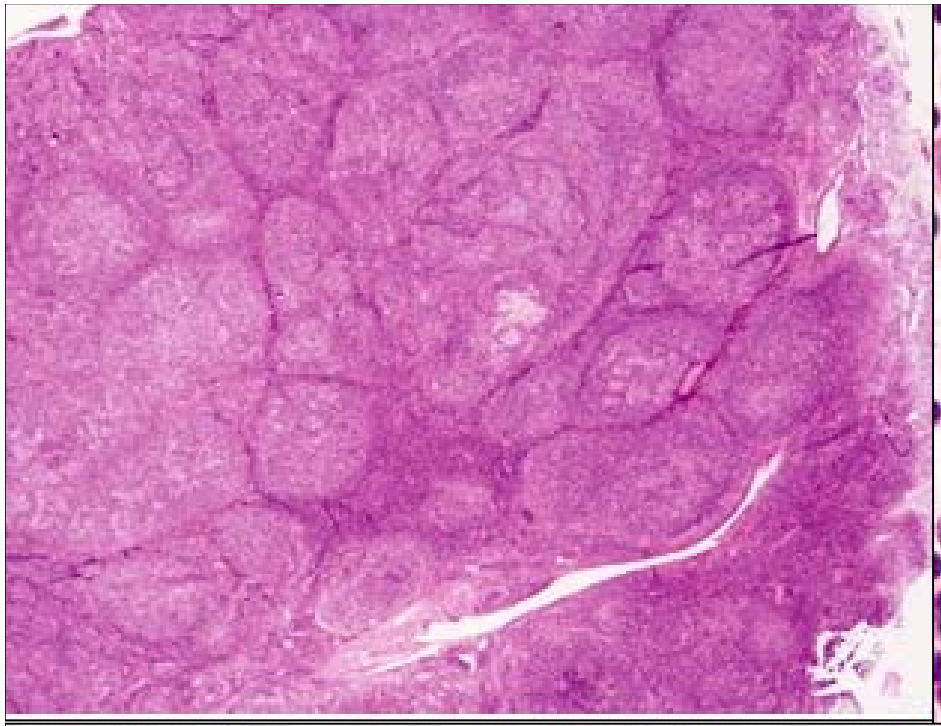
A B

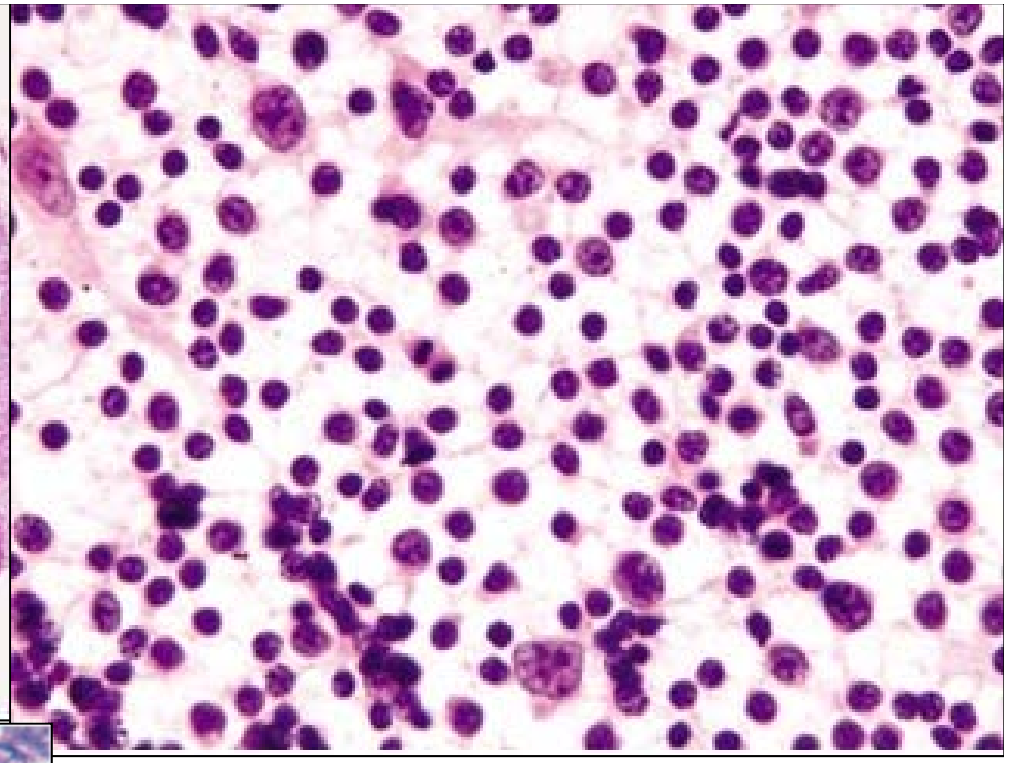


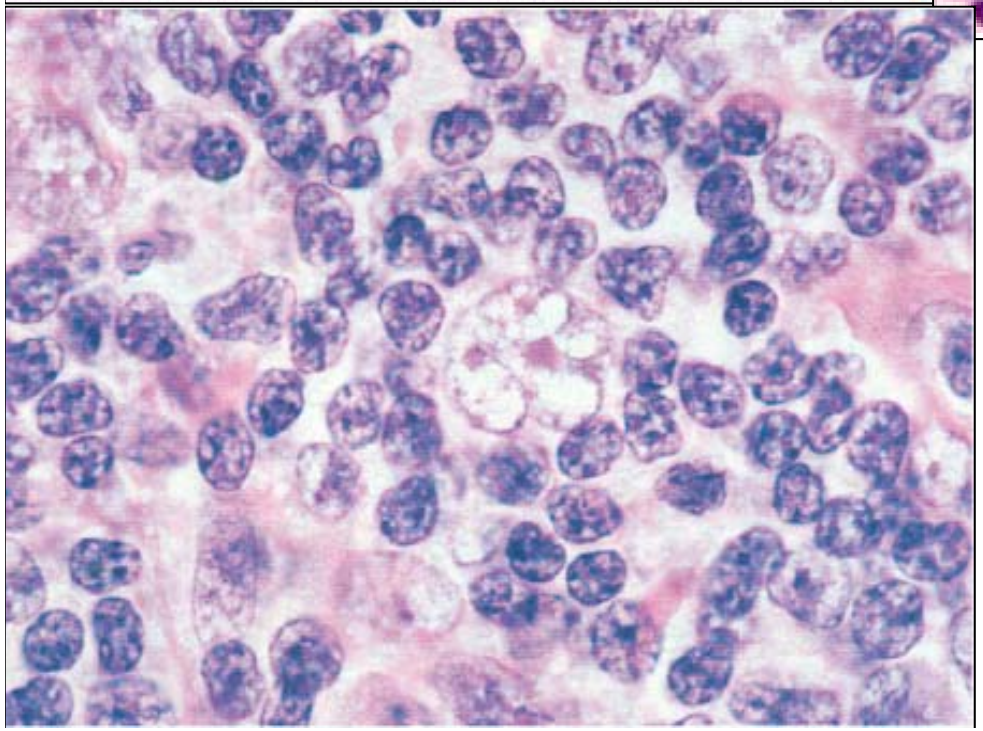
Jackson-Parker (1944)	Lukes-Butler (1966)	Rye (1966)	REAL (1994)	WHO classification (2008)	
Paragranuloma	Lymphocytic &/or histiocytic -Nodular -diffuse	Lymphocyte predominance	Nodular lymphocyte predominance	**Nodular lymphocyte predominance**	
			Classical HL	Lymphocyte rich	**CL**
Granuloma	Nodular sclerosis	Nodular sclerosis	Nodular sclerosis	Nodular sclerosis	**ASS**
	Mixed cellularity	Mixed cellularity	Mixed cellularity	Mixed cellularity	**ICA**
Sarcoma	Diffuse fibrosis	Lymphocyte depleted	Lymphocyte depleted	Lymphocyte depleted	**L**
	Reticular				

Nodular Lymphocytic Predominance HL

- The predominant cell is small B lymphocyte with or without an accompanying population of benign appearing histiocytes.
- L. node architecture is partially or totally effaced and infiltrate has a nodular pattern of growth,
- Nodularity is so pronounced as to simulate on low power the apperance of follicular lymphoma, but nodules of this disease are more irregular in size and staining quality with admixture of lymphocyte epitheloid cells gives them a mottled appearance, eosinophils, plasma cells, foci of fibrosis are scanty or absent.
- There is a large number of type of R.S.cell k.a. **'Popcorn' cells-characterized** by folded multilobed nucleus with smaller nucleoli. If numerous typical R.S. cells are found in lymphocyte predominant background, then case probably belongs to lymphocyte-rich type.
- There is convincing evidence that the lymphoma has origin from germinal centre cell at the cetroblastic stage of differentiation.







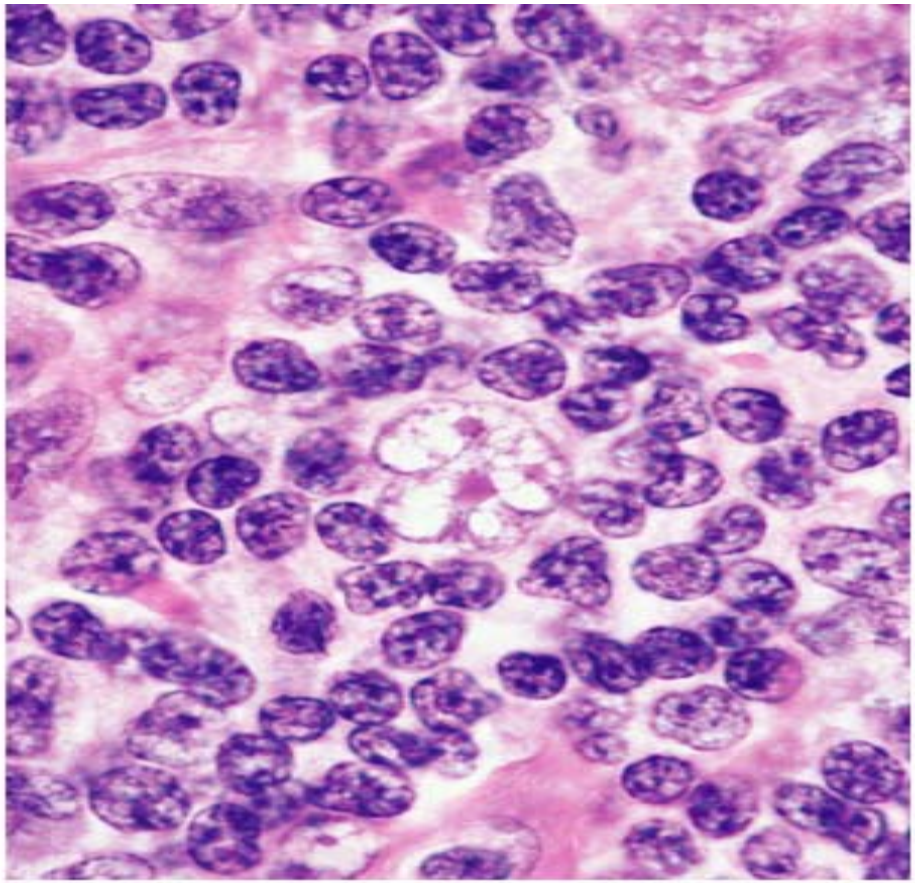
Lymphocyte predominant Hodgkin Lymphoma

- Immunophenotype of LP cells
- Positive markers:

- **CD20, CD79a**, CD75 ,**BCL6**, CD45
- EMA- 50%
- OCT-2, BOB.1, Activation induced deaminase
- Ig light and/or heavy chain- strong
- IgD-9-27%, more common in young males
- Ki-67 nuclear positivity

- Lack CD15 and CD30

Lymphocyte predominance Hodgkin's lymphoma. Showing the lymphocytic and/or histiocytic (L&H) type of cell ("popcorn" cell) that is characteristic of this condition.



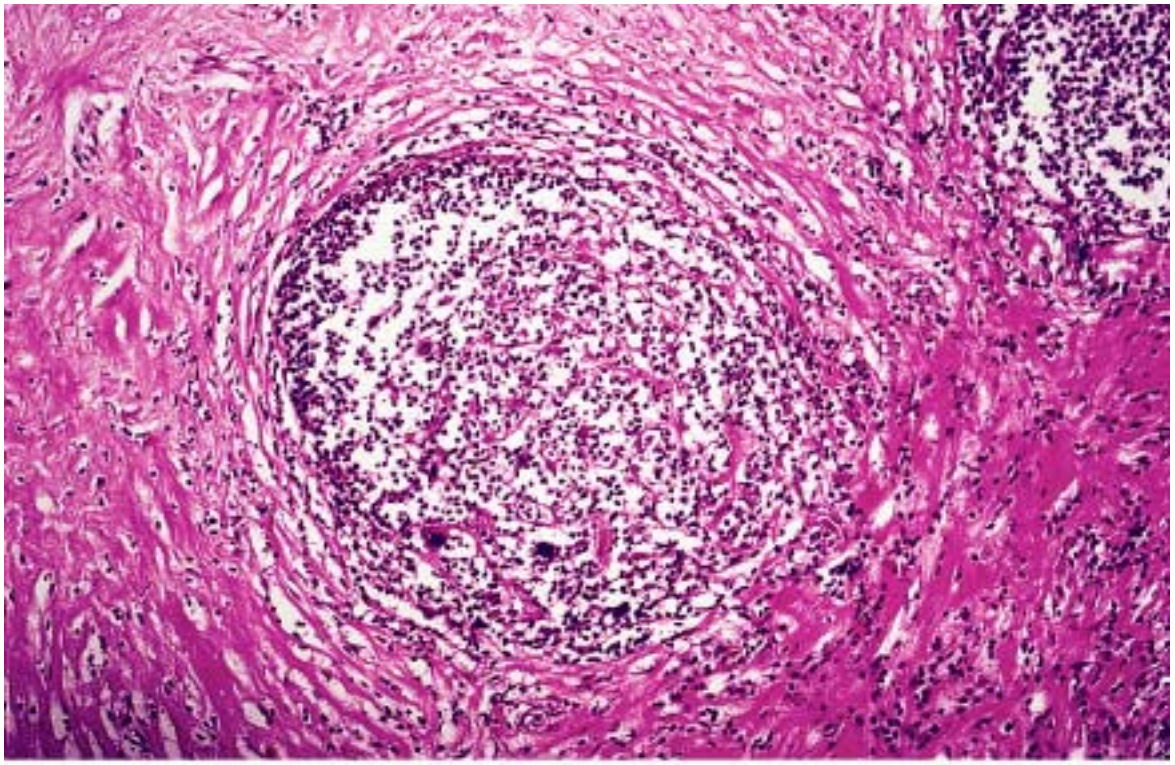
Nodular Sclerosis HL

- Characterized in its fully developed stage by broad collagen bands separating the lymphoid tissue in well defined nodules.

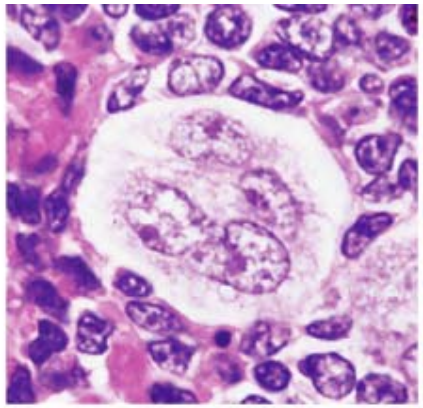
- In addition to the classic R.S. cells, the lymphoma displays a variant of R.S. cell k.a. ***lacunar cells*****.** This is quite large (40-50µm) with an abundant clear cytoplasm and multilobulated nuclei having complicated infoldings and nucleoli are smaller in size than those of classic R.S. cells.

- In some cases there is clustering of these lacunar cells around necrosis, they form sheets and cohesive nests to the point that a mistaken ∆is of large cell NHL, carcinoma, germ cell tumour, thymoma can be made. This type of nodular sclerosis is k.a. sarcomatous/ syncytial variants.

A well-developed case of nodular sclerosis Hodgkin's lymphoma. The lymphoid nodule is encased in dense fibrohyaline tissue



Various appearances of *lacunar cells* in nodular sclerosis HL



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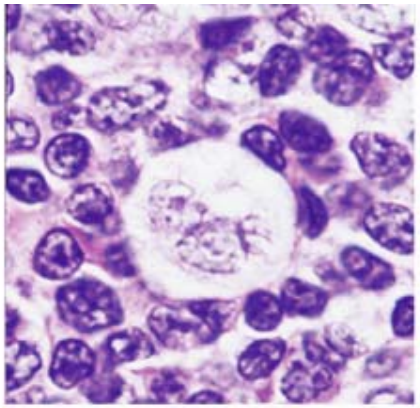

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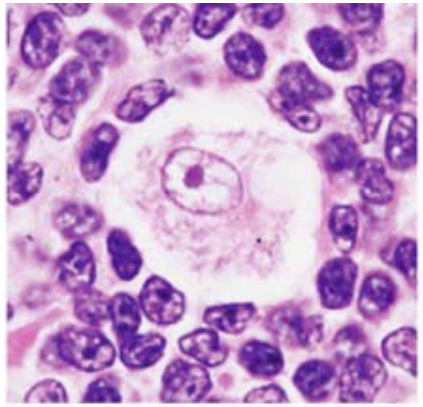

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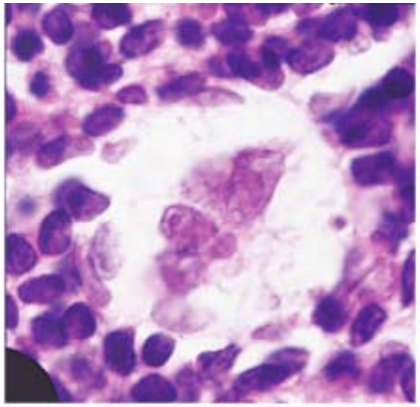

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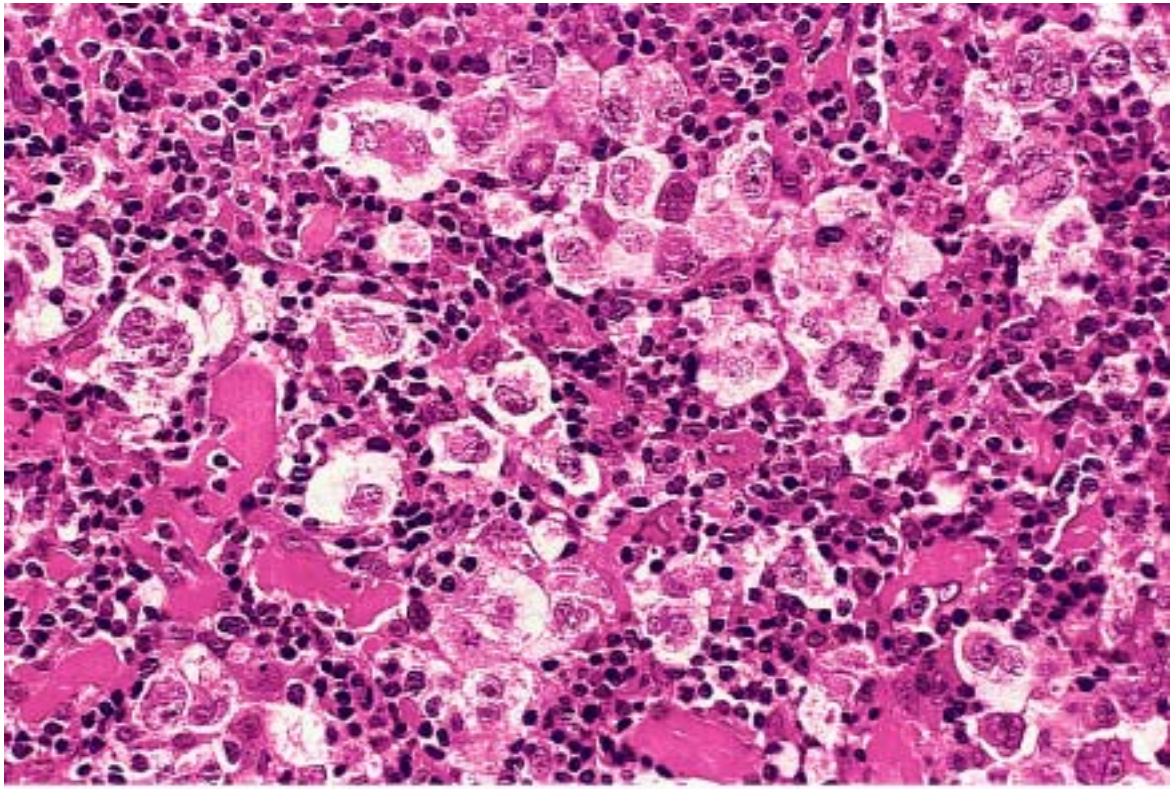
Cellular phase of nodular sclerosis HL.

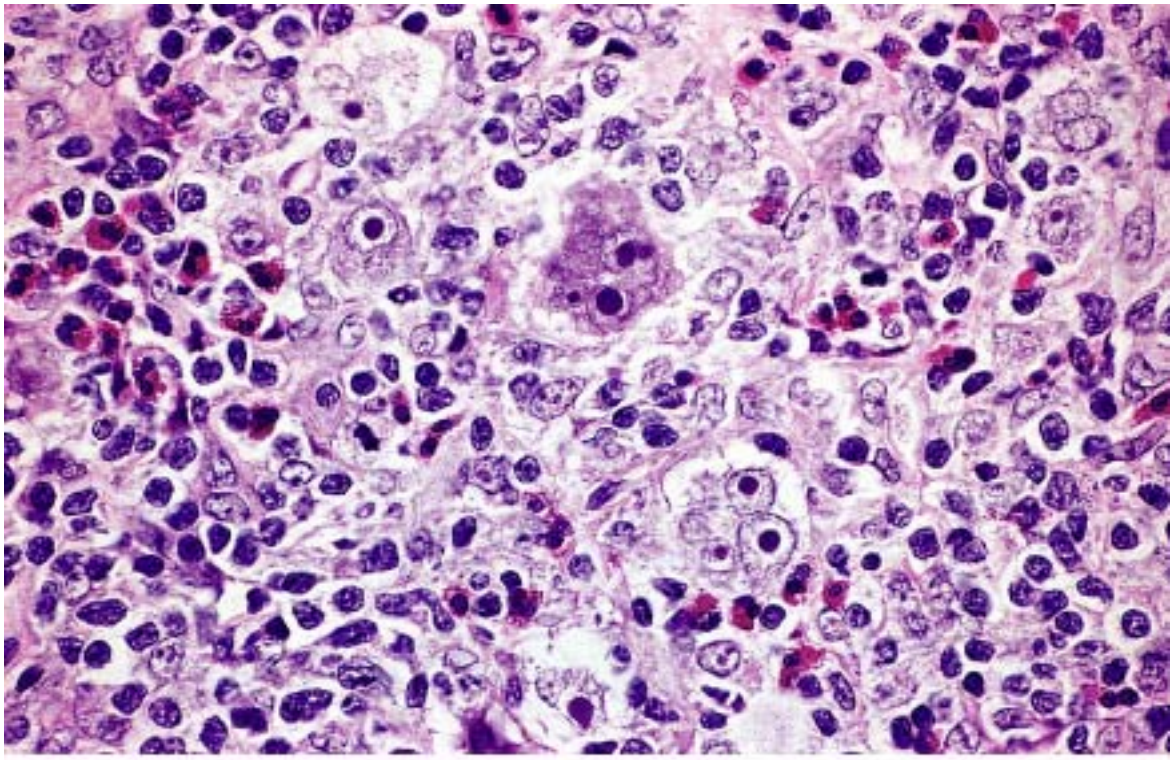
Lacunar cells are plentiful



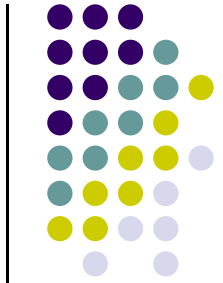
Mixed Cellularity HL

Have large number of eosinophils, plasma cells, atypical mononuclear cells admixed with classic R.S. cells, which tend to numerous, necrosis is present but fibrosis is normal.

Mixed cellularity HL.
Several diagnostic Reed–Sternberg cells are seen admixed with a polymorphic lymphoid infiltrate rich in eosinophil



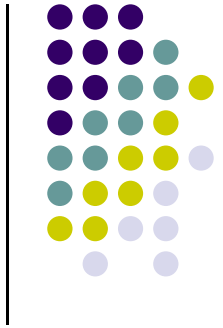
Lymphocyte-Rich HL



There is presence of R.S. cells scattered against a nodular or diffuse background largely composed of small lymphocytes and practically devoid of eosinophils and neutrophils.

The main D/D is with NLPHD which shows popcorn cells where as it shows R.S. cells.

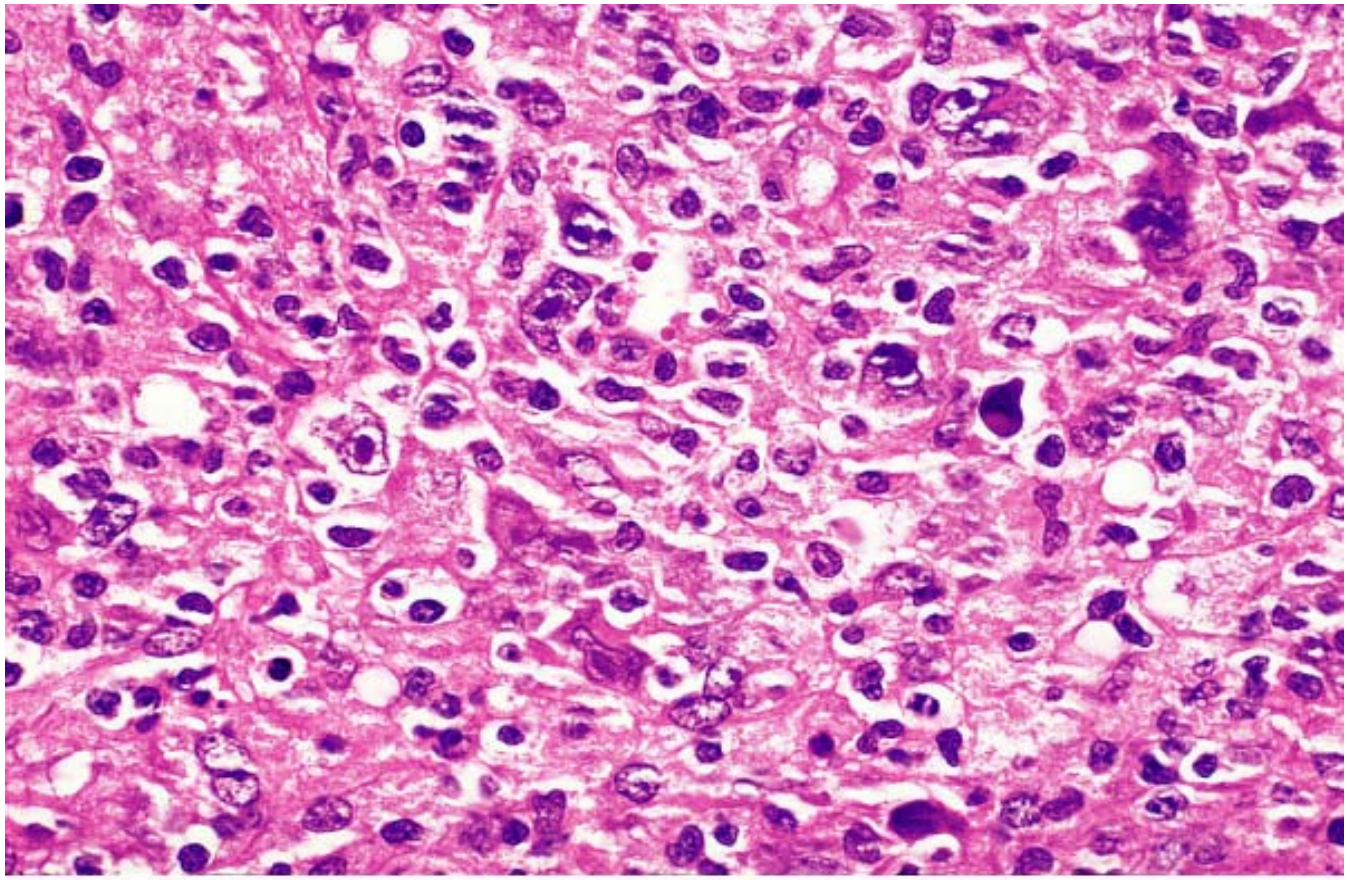
Lymphocyte-Depletion HL



Which comprises less than 5%; have 2 morphologic subtypes

- Diffuse fibrosis: there is heavy deposition of collagen fibers, number of lymphocytes and other cells are varying in number.
- Reticular subtype: is characterized by large number of diagnostic R.S. cells among atypical mononuclear cells, areas of necrosis is common.
- It should be remembered that patient with HL may develop in to NHL or leukemia either spontaneously or as a result of therapy.

Lymphocyte depletion type of HL. Numerous atypical cells are present in a densely fibrotic stroma. Lymphocytes are scanty



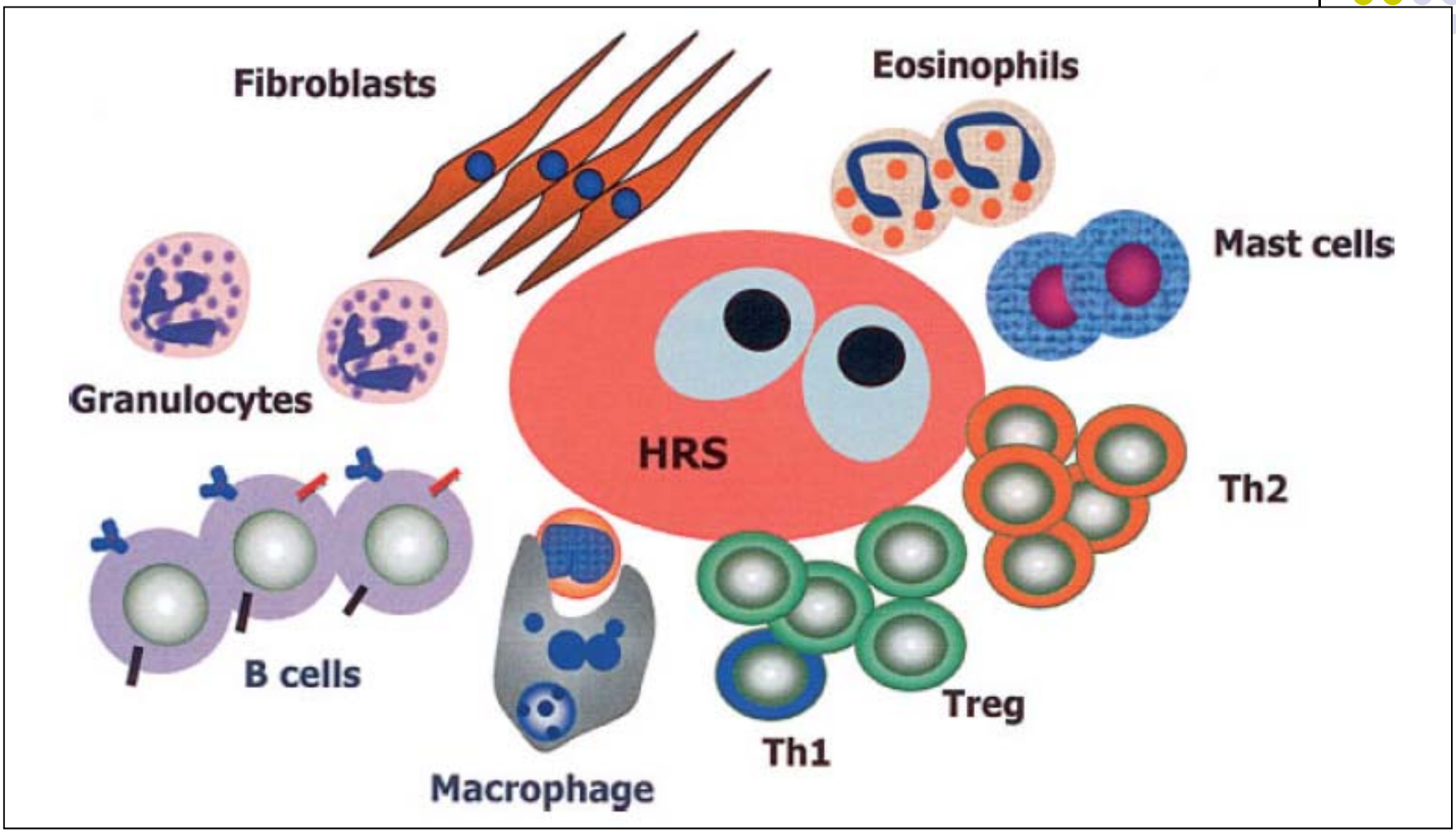
Biology of HRS

- HRS cell origin: B-cell at the germinal centre stage
- Lymphoma cells undergo **reprogramming** of gene expression
- Loses the typical B cell surface and functional phenotype
- Retain B-cell features associated with antigen presenting functions and interaction with Th cells
- Display an abnormal repertoire of membrane markers & transcriptional regulator of multiple lympho-haematopoietic cell types

Microenvironment

- Cellular components
- Non-neoplastic B and T small lymphocytes
- Plasma cells
- Neutrophils
- Eosinophils
- Mast cells
- Histiocytes/ reticulum cells
- Fibroblasts
- Non cellular components
- Extracellular matrix components - fibronectin, tenascin
- Neo-angiogenesis

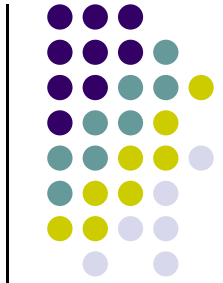
Hodgkin lymphoma microenvironment



Microenvironment formation

- HRS cells are regulated by interactions among tumor cells and reactive cells
- Essential for :
- **Tumor cell growth and survival**
- **To evade the host immune response**

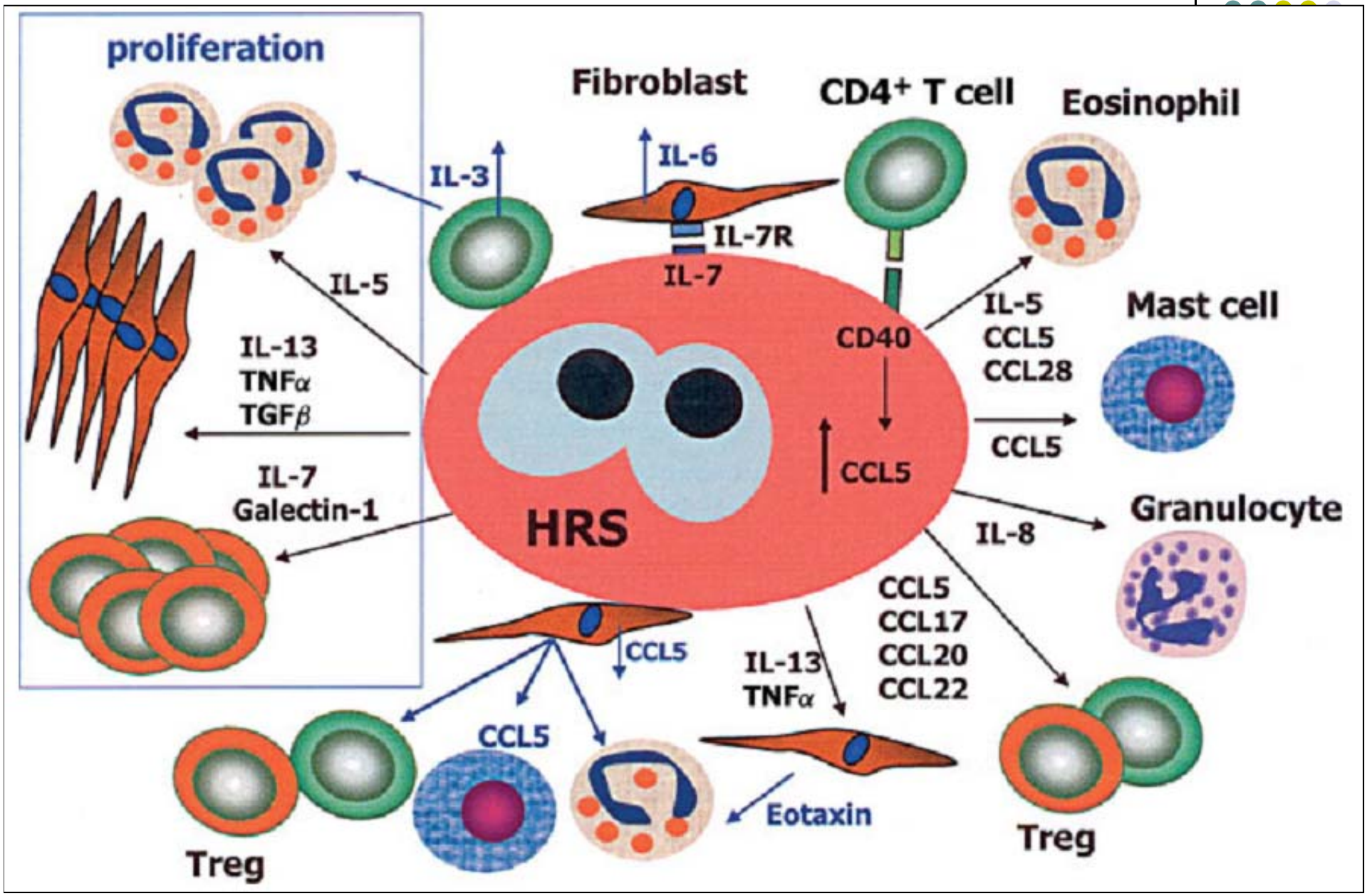
- Non-malignant cells are recruited and/or induced to proliferate by tumor cells
  - Cytokines & chemokines
  - Receptors in HRS cells



- TH2 cells and TReg cells: CCL5 (RANTES), CCL17, CCL22, CCL20
- Eosinophils: IL-5, CCL5, CCL28, eotaxin and GM- CSF
- Mast cells: CCL5
- Neutrophils : IL-8
- Fibroblast : TNF α, IL-13, TGF β and b FGF
- Plasma cells: CCL28
- Macrophages : GM-CSF

- EBV infection: IL-10, CCL5, CCL20 and CXCL10

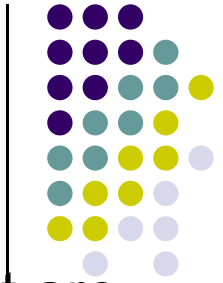
Microenvironment formation



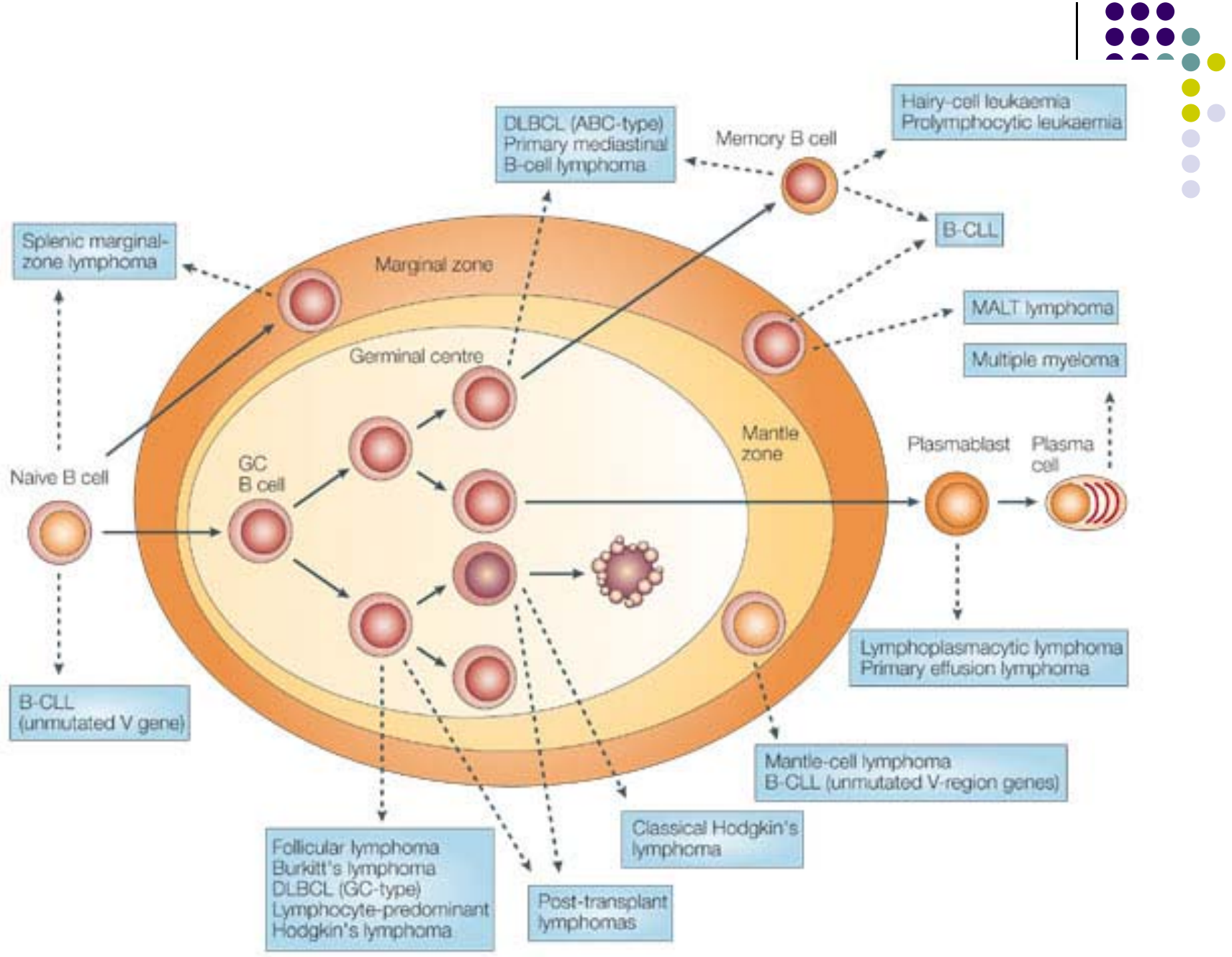
Microenvironment molecules as prognostic markers

- **Adverse outcome**
- IL-10
- IL-6
- CD30
- TARC/CCL17
- BAFF- resistance to therapy
- Soluble IL-7- advanced stages & presence of B symptoms

Non-Hodgkin Lymphoma (NHL)



- A heterogeneous group of B- and T-cell malignancies that are diverse in cellular origin, morphology, cytogenetic abnormalities, response to treatment, and prognosis
- Non-Hodgkin's Lymphoma (NHL)
  - 75% of lymphomas
  - 6th major cause of cancer deaths yearly
- Origin
- principally B-cells derivation (>85%)
  - T-cells derivation
  - Histiocytes (very rarely)
- Predominates in the 40-70 years age group
- Slight male predominance overall


DLBCL (ABC-type)
Primary mediastinal
B-cell lymphoma
Memory B cell
Hairy-cell leukaemia
Prolymphocytic leukaemia
Splenic marginal-
zone lymphoma
Marginal zone
B-CLL
MALT lymphoma
Germinal centre
Multiple myeloma
Mantle
zone
Plasmablast
Plasma
cell
Naive B cell
GC
B cell
Lymphoplasmacytic lymphoma
Primary effusion lymphoma
B-CLL
(unmutated V gene)
Mantle-cell lymphoma
B-CLL (unmutated V-region genes)
Classical Hodgkin's
lymphoma
Follicular lymphoma
Burkitt's lymphoma
DLBCL (GC-type)
Lymphocyte-predominant
Hodgkin's lymphoma
Post-transplant
lymphomas

- Precursor B cell -
- Naïve B cells -
- Mantle cell -
- Centroblasts -
- Centrocytes -

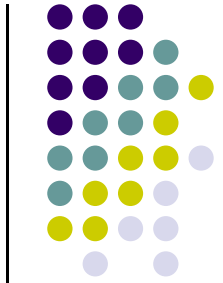
- Marginal zone cells

- Plasma cells

REAL/WHO Classification of NHL

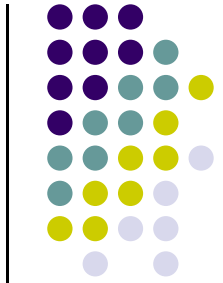
- **B-CELL LYMPHOMAS** (>85%)
  - **Precursor B-cell neoplasms**
    - Precursor B lymphoblastic leukemia/lymphoma
  - **Mature B-cell neoplasms**
    - **Diffuse Large B-Cell Lymphomas (31%)**
    - Follicular Lymphoma (22%)
    - Mucosa-Associated Lymphatic Tissue (MALT) Lymphoma (7.5%)
    - Small Lymphocytic Lymphoma-Chronic Lymphocytic Leukemia (7%)
    - Mantle Cell Lymphoma (6%)
    - Mediastinal (Thymic) Large B-Cell Lymphoma (2.4%)
    - Burkitt Lymphoma-Burkitt Leukemia (2.5%)
    - Lymphoplasmacytic Lymphoma-Waldenstrom Macroglobulinemia (<2%)
    - Nodal Marginal Zone B-Cell Lymphoma (<2%)
    - Splenic Marginal Zone Lymphoma (<1%)
    - Hairy cell leukemia

REAL/WHO Classification of NHL



- Mature B-cell neoplasms (contd)
  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma
  - Extranodal Marginal Zone B-Cell Lymphoma (<1%)
  - Intravascular Large B-Cell Lymphoma (<1%)
  - Primary Effusion Lymphoma (<1%)
  - Lymphomatoid Granulomatosis (<1%)

REAL/WHO Classification of NHL



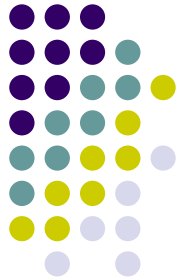
- **T-CELL and NK CELL NEOPLASMS**
  - **Precursor T-cell neoplasms**
    - Precursor T lymphoblastic leukemia/lymphoma
    - Blastic NK cell Lymphoma
  - **Mature T and NK Cell Lymphomas (~12%)**
    - Extranodal T or NK-Lymphoma
    - Cutaneous T-Cell Lymphoma (Sézary Syndrome and Mycosis Fungoides)
    - Anaplastic Large Cell Lymphoma
    - Angioimmunoblastic T-Cell Lymphoma
    - T-cell prolymocytic Lymphoma
    - T-cell large granular lymphocytic leukemia
    - Adult T-cell leukemia/Lymphoma
    - Enteropathy-type T-cell Lymphoma
    - Hepatosplenic T-cell Lymphoma
    - Subcuataneous panniculitis-like T-cell Lymphoma
    - Primary Cutaneous anaplastic large cell lymphoma
    - Peripheral T-cell Lymphoma, Unspecified

Precursor B & T lymphoblastic leukemia/lymphoma

- B-ALL peaks in incidence at about the age of 3, perhaps because the number of normal bone marrow pre-B cells (the cell of origin) is greatest very early in life.
- the peak incidence of T-ALL is in adolescence, the age when the thymus reaches its maximal size.
- B- and T-ALL also occur less frequently in adults

- In leukemic presentations, the marrow is hypercellular and packed with lymphoblasts, which replace the normal marrow elements.
- Mediastinal thymic masses occur in 50% to 70% of T-ALLs, which are also more likely to be associated with lymphadenopathy and splenomegaly.

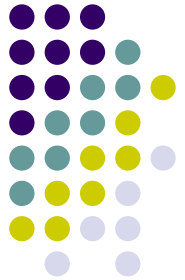
CLINICAL FEATURES



- *Abrupt stormy onset* within days to a few weeks of the first symptoms •
- ***Symptoms related to depression of marrow function***, including fatigue due to anemia; fever, reflecting infections secondary to neutropenia; and bleeding due to thrombocytopenia

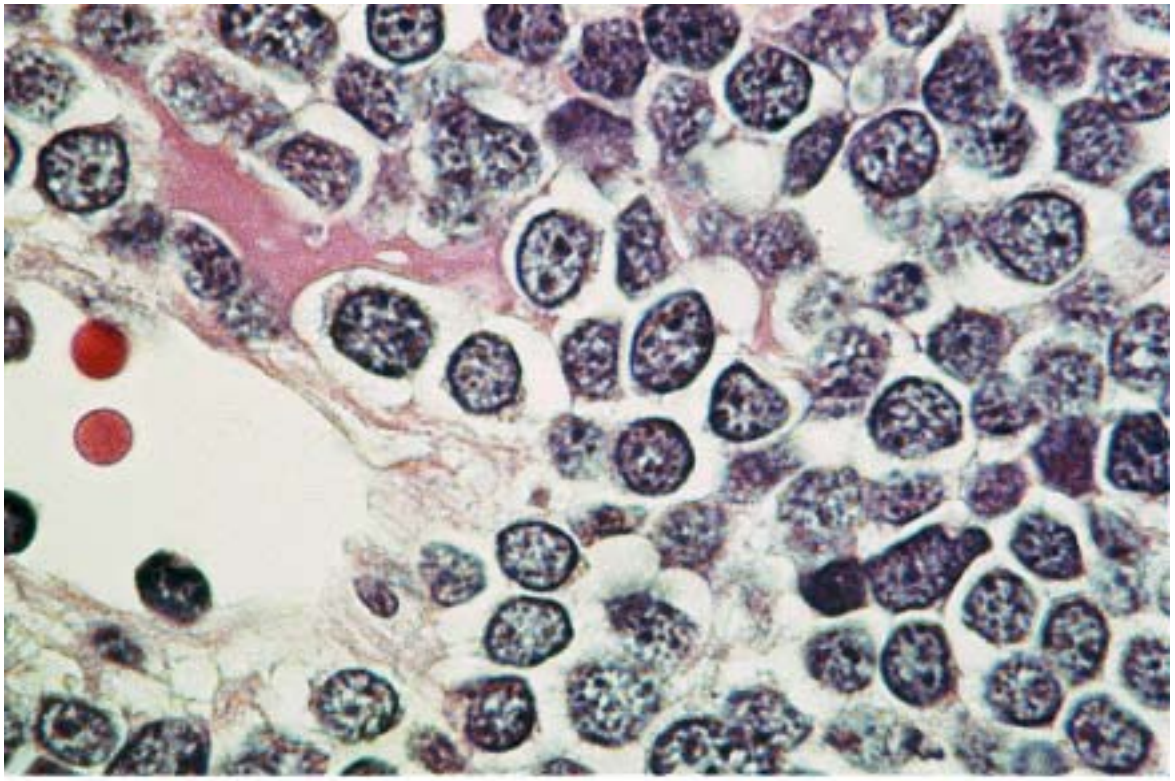
- ***Mass effects caused by neoplastic infiltration*** (which are more common in ALL), including bone pain resulting from marrow expansion and infiltration of the subperiosteum; generalized lymphadenopathy, splenomegaly, and hepatomegaly; testicular enlargement; and in T-ALL, complications related to compression of large vessels and airways in the mediastinum •
- ***Central nervous system manifestations*** such as headache, vomiting, and nerve palsies resulting from meningeal spread, all of which are also more common in ALL

MORPHOLOGY



- In both B- and T-ALL, the tumor cells have scant basophilic cytoplasm and nuclei somewhat larger than those of small lymphocytes
- The nuclear chromatin is delicate and finely stippled, and nucleoli are either absent or inconspicuous.

Lymphoblastic lymphoma. In this example the nuclear convolutions are barely evident



- the mitotic rate is high. As with other rapidly growing lymphoid tumors, interspersed macrophages ingesting apoptotic tumor cells may impart a “starry sky” appearance

- lymphoblasts are myeloperoxidase-negative and often contain periodic acid–Schiff-positive cytoplasmic material.

- Immunophenotype.

  Immunostaining for terminal deoxynucleotidyl-transferase (TdT), a specialized DNA polymerase that is expressed only in pre-B and pre-T lymphoblasts, is positive in more than 95% of cases

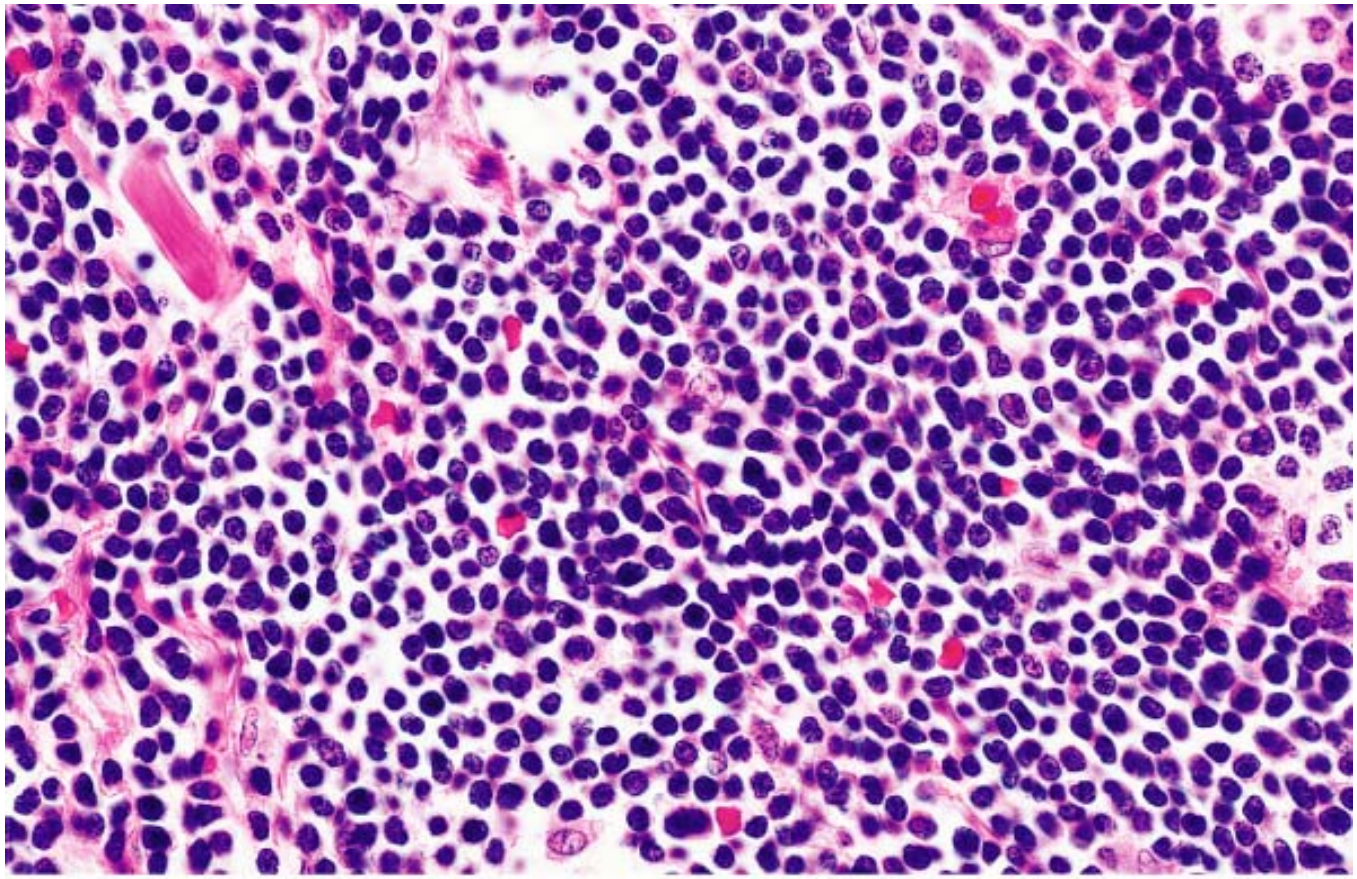
Small Lymphocytic Lymphoma (SLL)/ Chronic Lymphocytic Leukemia (CLL)

- These two disorders are morphologically, phenotypically and genetypically indistinguishable, differing only in the degree of peripheral blood lymphocytosis.
- Most patients have sufficient lymphocytosis to fulfill the diagnostic requirement of CLL (absolute lymphocyte count >5000/cumm) which is the most common leukemia of adults.
- In contrast, SLL constitutes only 4% of NHL

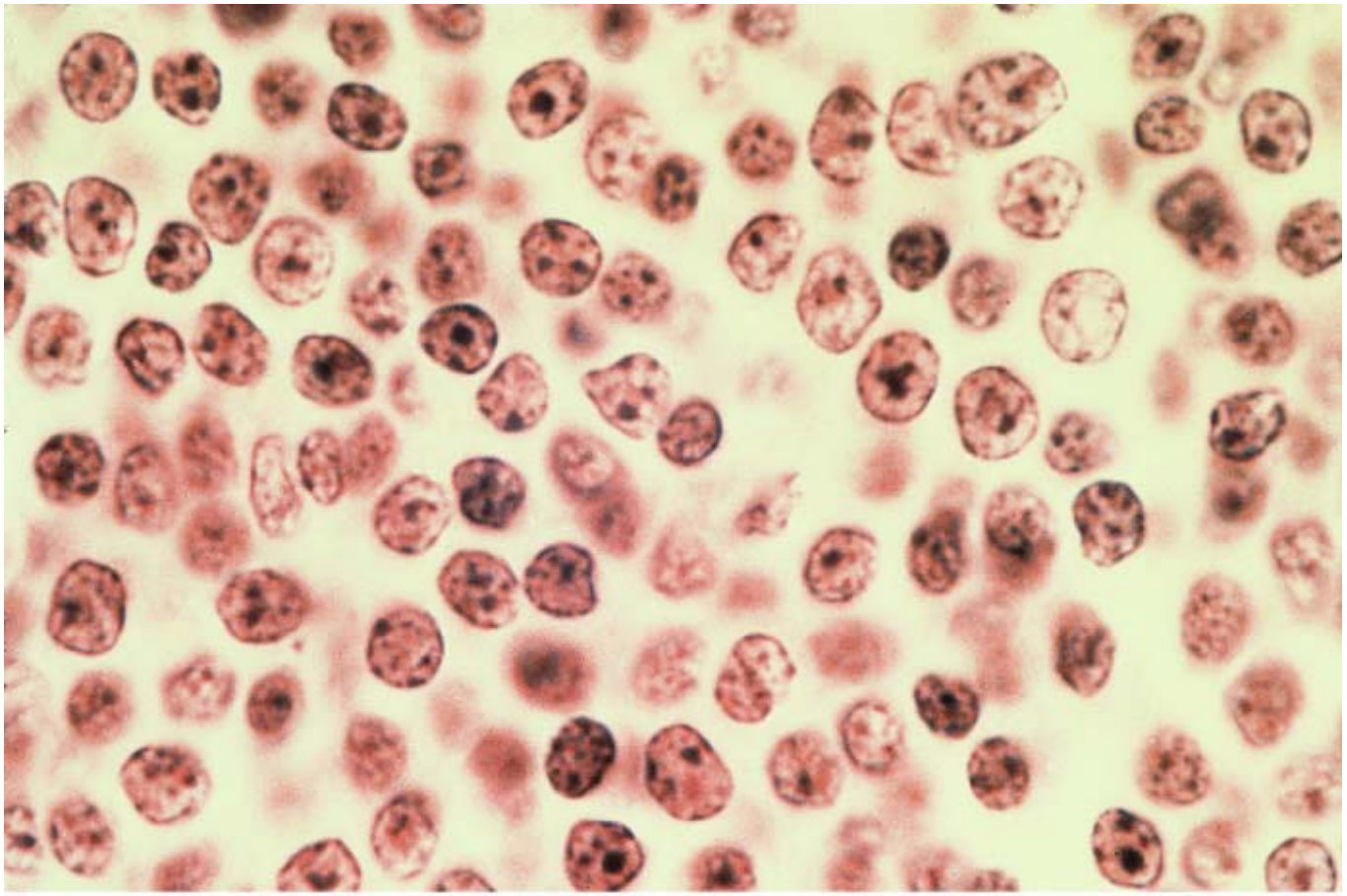
- **C/F**-Age: >50 years, M>F,
  - Patients are often asymptomatic, when symptoms present they are non-specific, generalized LAP, hepatosplenomegaly are seen (50-60%).
  - pts with CLL usually have WBC count >2,00,000/cumm
  - Hypogammaglobinemia is common- ↑ed infection
  - 10-15%pts P/C Autoimmune hemolytic anemia or thrombocytopenia
  - Prognosis-variable, median survival is 4-6 years

- **Morphology-**
  - L. node architecture is diffusely effaced by a predominant population of S. lymphocytes (6-12µm) containing round to slightly irregular nuclei with condensed chromatin and scant cytoplasm.
  - In addition some time these cells are mixed with variable number of large cells called prolymphocytes (vesicular nuclei with prominent nucleoli). These **prolymphocytes**, if form loose aggregates focally referred to as proliferation centres, they contain cells showing high mitotic activity.
- **In CLL-** Peripheral blood contains increased number of small lymphocytes these cells are fragile, gets disrupted form **smudge cells.** All cases of CLL show involvement of BM and most of the cases of SLL

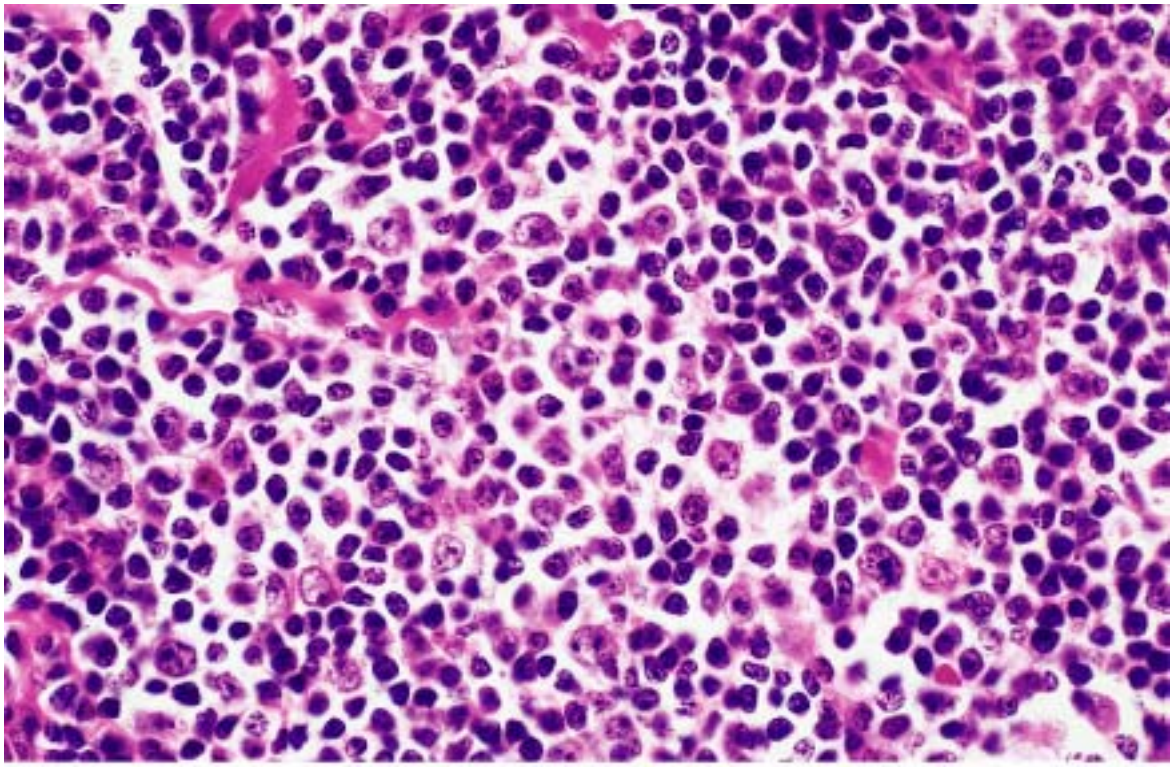
Low-power view of small lymphocytic lymphoma. A monotonous proliferation of small lymphocytes effaces the architecture of the node.



High-power view of small lymphocytic lymphoma. The nuclear contours are regular, the chromatin is clumped, and nucleoli are inconspicuous



So-called “growth center” in a lymph node involved by SLL



Transformation (of SLL/CLL) to other aggressive lymphoma

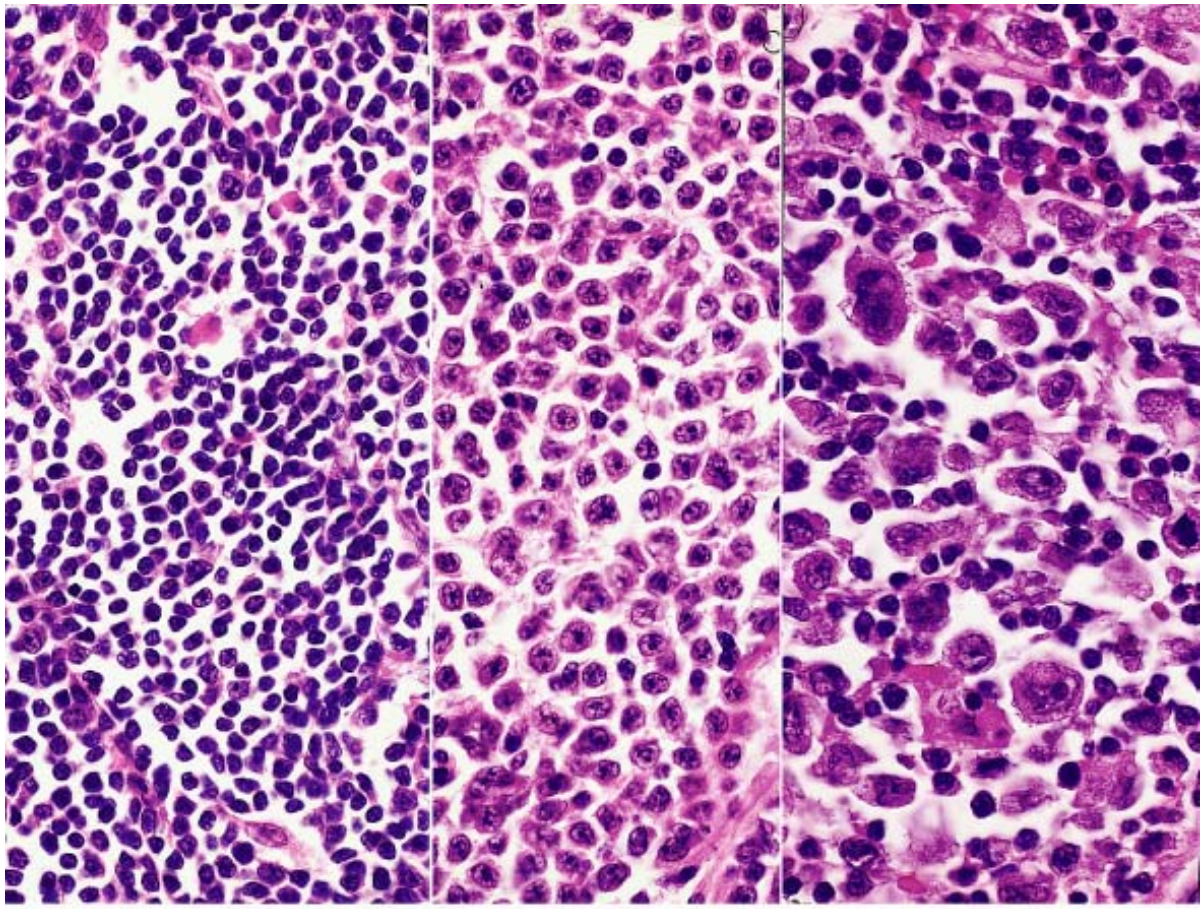
- **Prolymphocytic transformation_** (15-30%) cases- there is worsening of cytopenia, ↑ing splenomegaly, peripheral blood shows ↑ed number prolymphocytes
- **Richter syndrome-**(10%) cases- there is transformation in to diffuse large B cell lymphoma- there is appearance of a rapidly enlarging mass with in L. node and spleen and patients' survival becomes less than 1year
- Sometime SLL present with R.S. cells suggesting a possibility of transformation to **HL**

- Immuno-phenotype: express pan B-cell markers CD19, CD20, in addition –CD23, CD5.

- **Cytogenetics and molecular genetics-** chromosomal translocations are rare.
  - Most common findings are deletions of 13q12-14, deletion of 11q, trisomy 12q, and deletions of 17p. DNA sequencing suggests that cell of origin may be a postgerminal centre memory B-cell or naïve B-cell.

Various morphologic types of lymph node involvement by CLL. A, **monotonous infiltrate of small mature lymphocyte** B**. Somewhat immature forms with slightly large nuclei & more open chromatin.** C**. large pleomorphic cell (Richter's syndrome)**

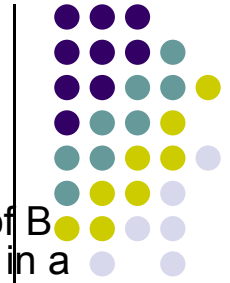
A B C



Follicular Lymphoma

- It is B-cell neoplasm that recapitulates the architectural and cytologic features of the normal secondary lymphoid follicles
- 40% of all NHL, occur in elderly, unusual under 20 yrs of age
- **Grossly and lower power-** shows nodular pattern of growth with progression –nodularity becomes blurred and eventually most of the proliferation shows a diffuse pattern
- Cytologically: shows mixture of different proportion of small and large lymphoid cells which resemble their normal follicular counterparts. The small cells have scanty cytoplasm and an irregular, elongated cleaved nucleus with prominent indentation and infoldings; the size is similar or slightly larger than that of normal lymphocytes, chromatin- coarse, nucleolus- inconspicuous. These cells are called centrocytes, or small cleaved follicular center cells
- Larger cells are 2-3 times the size of normal lymphocytes they have a distinct rim of cytoplasm, vesicular nucleus with one or three nucleoli often adjacent to the nuclear membrane, these cells represent the proliferating component of the tumour k.a. centroblasts, large (cleaved/non-cleaved) follicular central cells.
- Other large cell seen in follicular lymphoma is non-neoplastic dentritic follicular cells having finely dispersed chromatin, lack of identifiabl;e cell boundaries and the inconspicuous of the nucleolus.

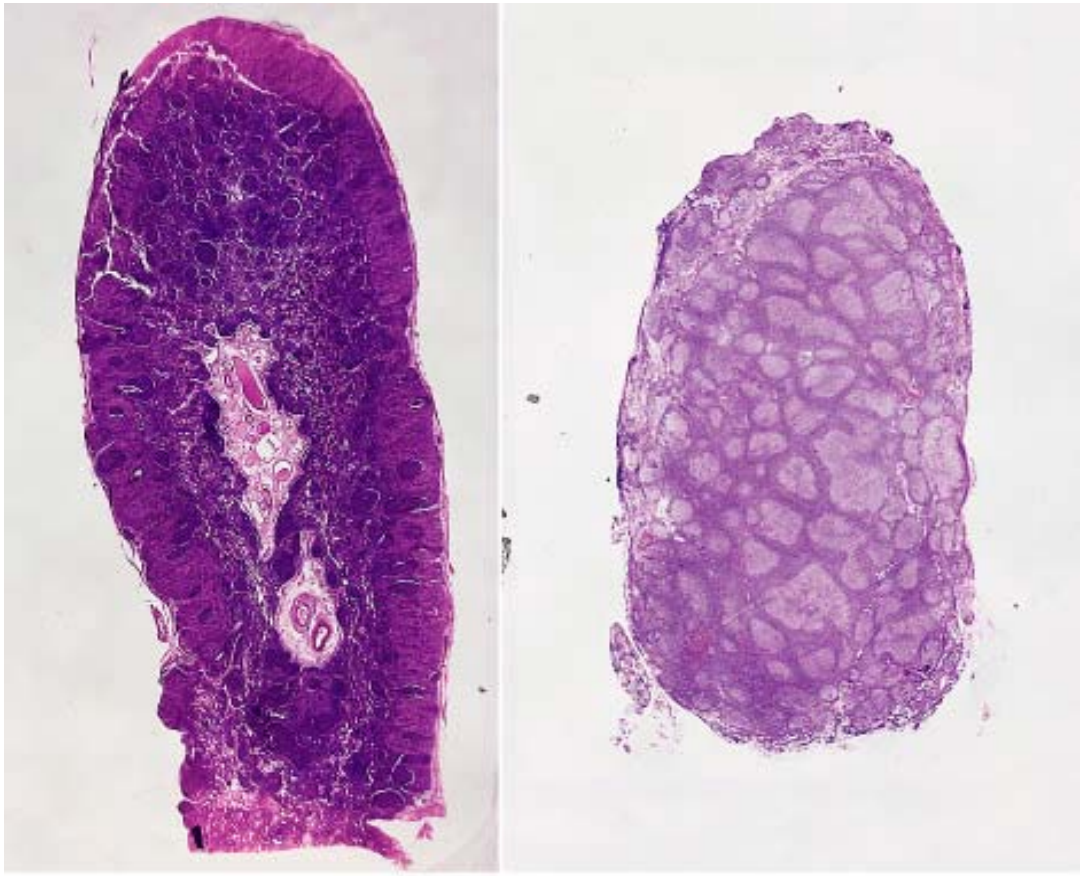
Follicular Lymphoma



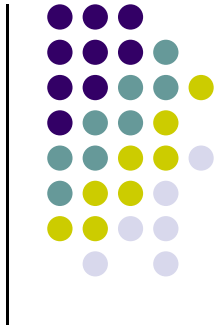
- Immunohistochemically- follicular lymphomas composed of monoclonal population of B cells admixed with non-neoplastic population of all the elements of normally present in a normal germinal center including follicular centre B cell, small T-cell, mac, and follicular dendritic cells. Tumour cells express pan B antigens CD19, CD20, CD12, CD74; also expresses surface or cytoplasmic Ig. CD5 and CD43 are usually negative.
- CD10-(CALLA) has been detected in 60-70% of cases, it is also used for D/D with follicular hyperplasia(-ve) and it is an indicator of follicle center origin if present in a diffuse large cell lymphoma.
- Cytogenetically-85% of cases have t(14;18) translocation . This results in the bcl-2 gene being translocated from its normal position on Ch.18 to Ch. 14.bcl-2 gene is an integral membrane protein located in inner mitochondrial membrane which functions as a suppressor of apoptosis. It is identified by Southern blot, PCR & immunochemistry, present in approximately 85% of follicular lymphoma and absent in follicular hyperplasia.
- Other translocation-t(8;14),rearrangement of bcl-6 located in chromosome 3q27
- Categories-depending upon –relative proportion of small and large cells. It is divided in to 3 categories
  1. Predominantly small cleaved cells, large cells are <20% (good prognosis)
  2. Mixed population Large cells are 20-50%
  3. Predominantly large cells 50% (worse prognosis)
  4. A 4th category in which neoplastic follicles are entirely composed of small lymphocytes. Extranodal spread- spleen, liver, bone marrow, skin.

Even distribution of neoplastic follicles in follicular lymphoma (B), as opposed to the predominantly cortical distribution typical of follicular hyperplasia (A).

A B



Follicular Lymphoma



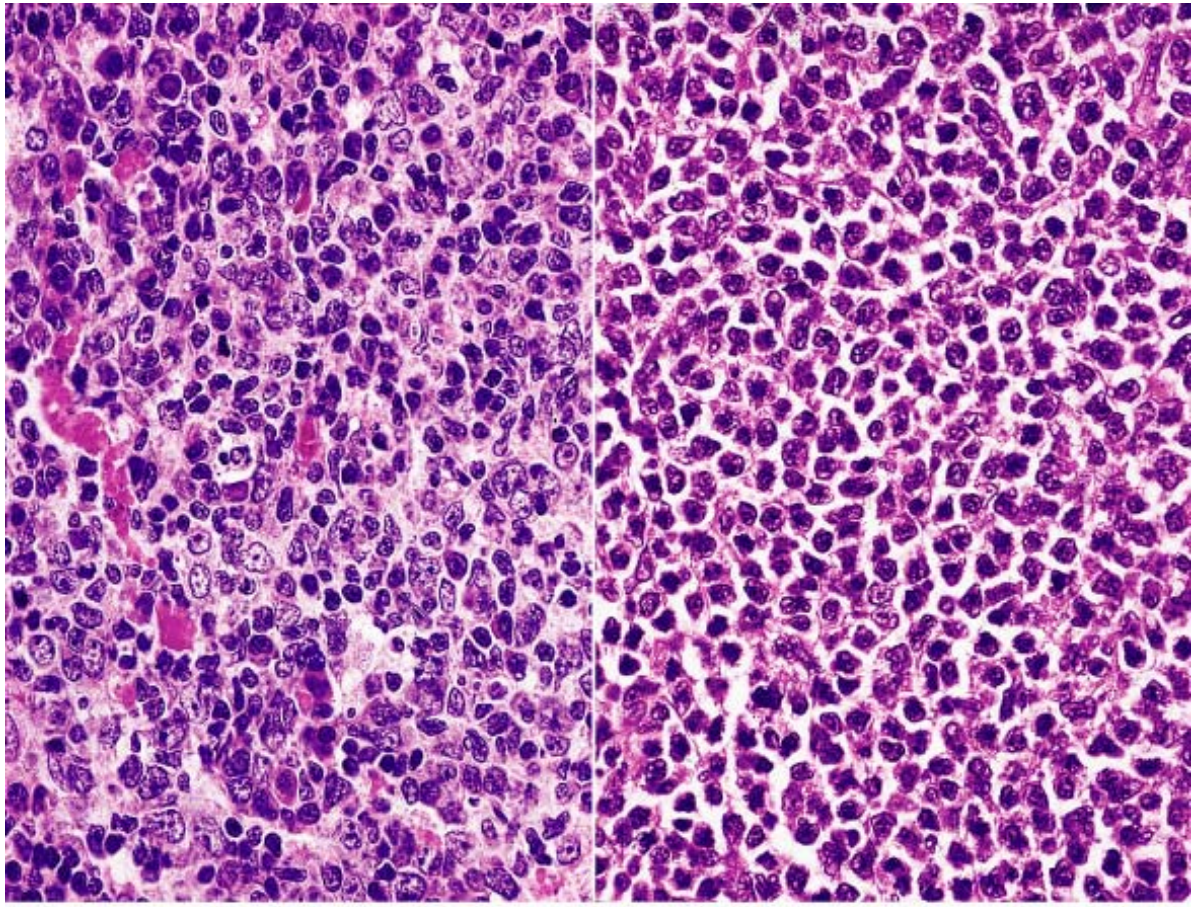
- Variations-morphological
  - Presence of fine or coarse bands of fibrosis that gives a nodular character of the lesion and may get confused with carcinoma
  - Presence of monocytoid B cells , seen in 10% of cases . Molecular studies have shown a common clonal origin of these cells from follicle center cells.
  - Deposition of proteineceous material in the centre of the nodules
  - Presence of large cytoplasmic eosinophilic globules that push the nucleus laterally and results a signet ring effect.
  - Plasmocytic differentiation in some or many of cells.
  - Permeation of the tumour follicle by small round lymphocytes of mantle zone region, the appearance simulating that of progressively transformed germinal centre (floral variant).
  - Presence of rosettes made up of cytoplasm and cytoplasmic processes of the lymphoid tumour cells.
  - Inversion of the usual staining pattern as seen in low power, the neoplastic follicles appear darker than the surrounding lymphoid tissue . This pattern which is referred to as reverse or inverse variant of follicular lymphoma, have no prognostic significance.
  - Prominent epitheloid grannulomateous response

Follicular Lymphoma

- **C/F:** painless generalized LAP, involvement of extranodal site such as- such as GIT, CNS, testis- relatively uncommon- it is incurable but follows indolent waxing and waning course.
- Median survival is 7-9year and is not improved by aggressive therapy. So T/T approach is low dose chemotherapy/radiotherapy, when pt becomes symptomatic
- Histologic transformation occurs in 30-50% of cases most commonly to diffuse large b-cell lymphoma. Rarely it transform to an aggressive tumour resembling Burkitt's lymphoma. Median survival is less than I year after transformation
- P/blood- involvement produce lymphocytosis is seen in 10% of cases
- BM- 85% of cases
- Splenic and hepatic involvement is also frequently seen.

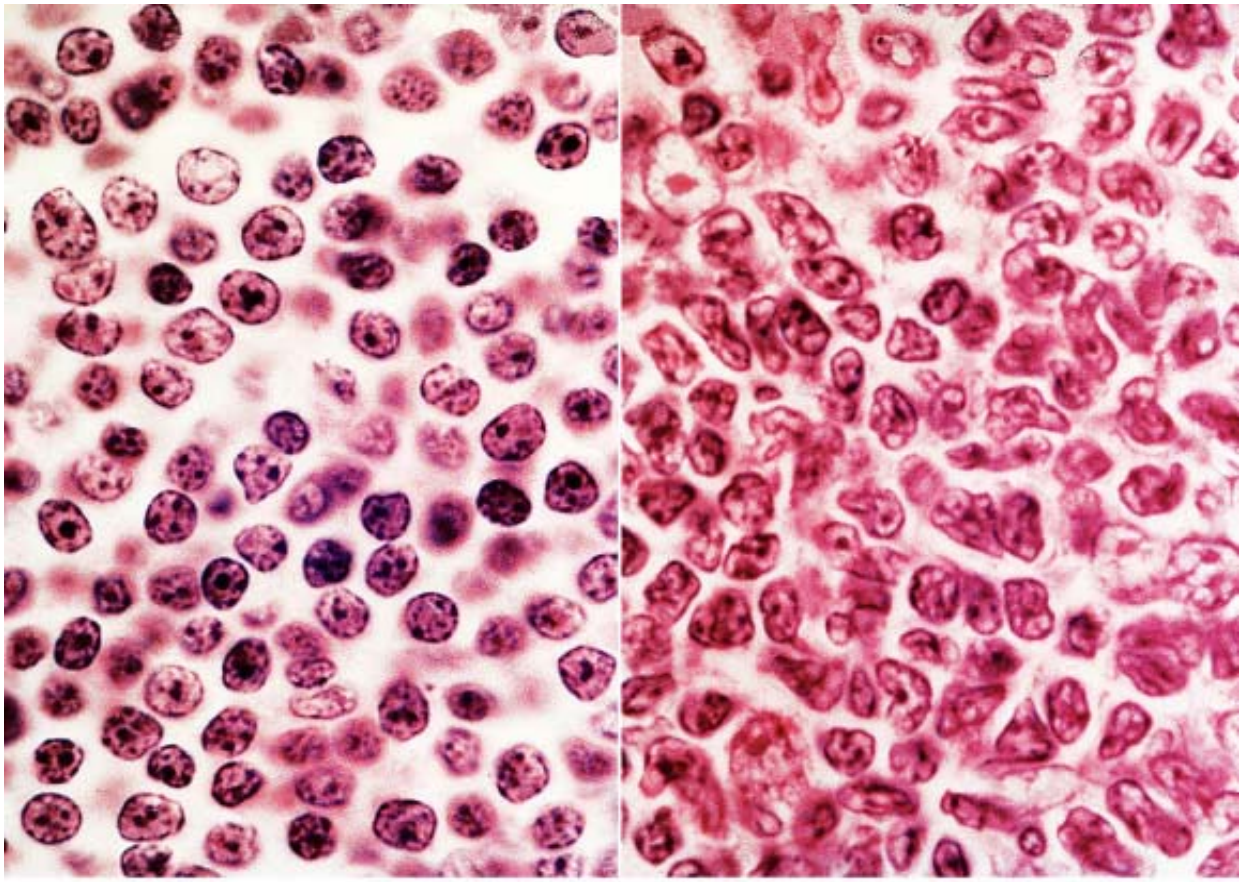
Homogeneous population of small cleaved cells in follicular lymphoma (B), as opposed to the polymorphic composition seen in follicular hyperplasia, including the presence of tingible-body macrophages (A).
follicular lymphoma

A B

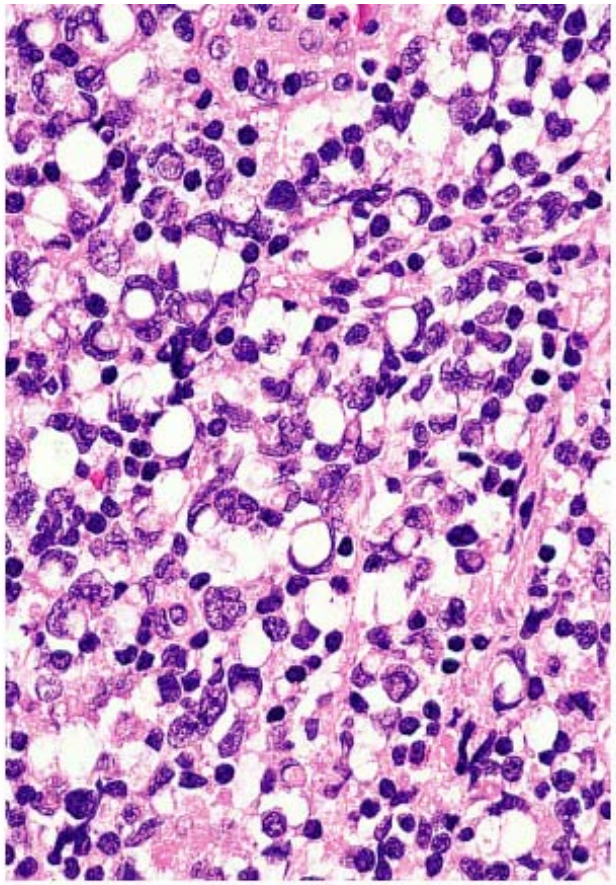


Marked contrast between the cleaved cells of follicular lymphoma (B) and the regular mature lymphocytes of small lymphocytic lymphoma (A)

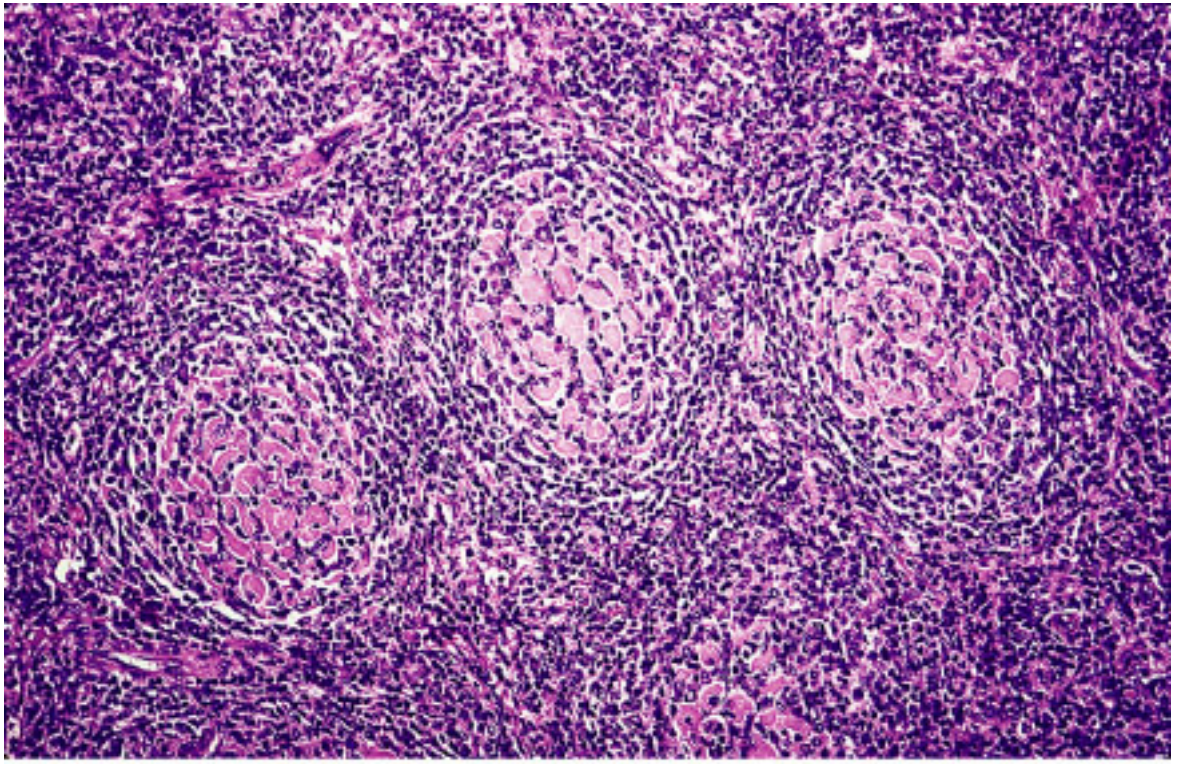
A B



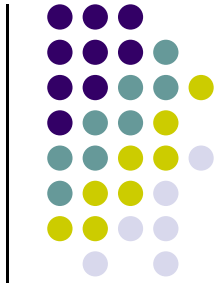
Malignant lymphoma featuring signet ring changes in some of the tumor cells.



Follicular lymphoma with deposition of proteinaceous material among the tumor cells. Ultrastructurally, some of this material was found to be within the cytoplasm of dendritic follicular cells.



Mantle Cell Lymphoma

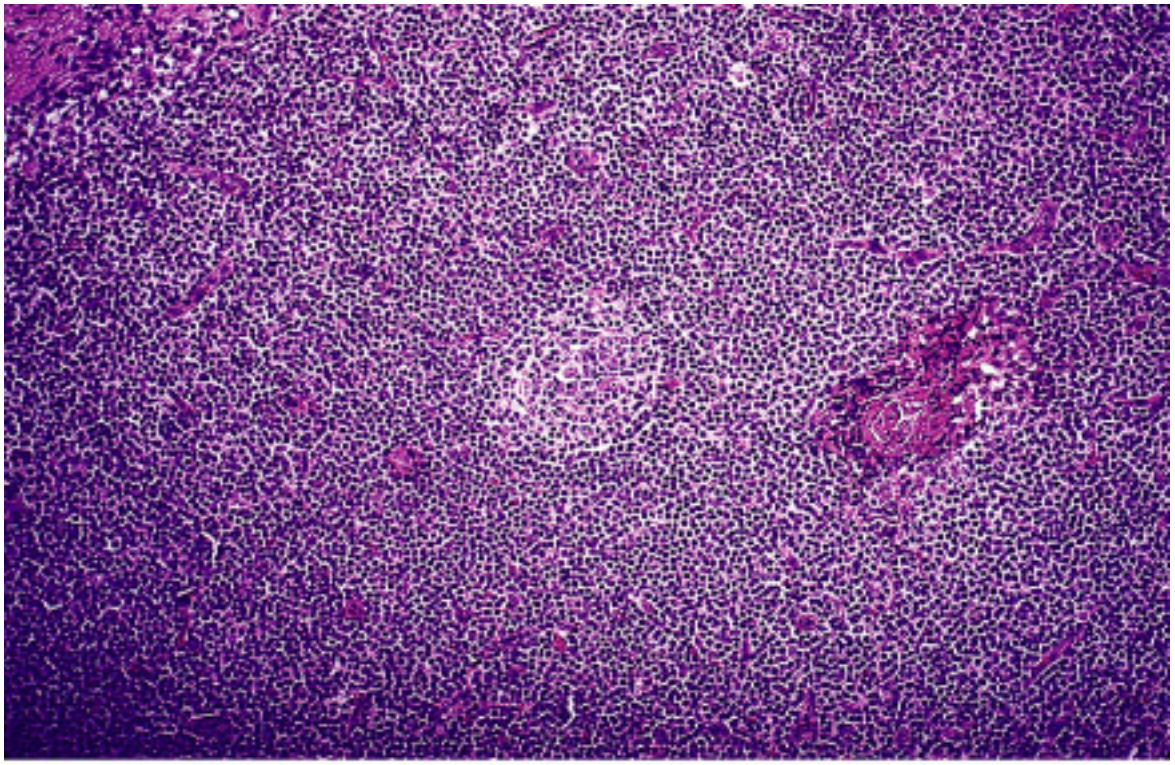


- Low grade lymphoma, it comprises 3-10% of all NHL
- Occurs in 5^{th}-6^{th} decade of life, shows male predominance
- The tumour cells closely resemble the normal mantle zone B-cells that surround the geminal centres
- Morphology- Tumours cells may be surround reactive/or residual germinal centres, producing a vaguely nodular appearance at low power or diffusely effaced nodal architecture. Typically population consists of a hemogenous population of small lymphocytes with round to irregular to occasionally deeply clefted nuclear contours.
- So most of the small lymphocytes are similar to those of SLL and other showing slightly irregular and indented nuclear contours resemble to small cleaved cells follicular lymphoma
- In some cases, tumour cells have large nuclei with more dispersed chromatin and higher proliferative factor k.a. blastic variant which is associated with BM and spleen involvement.

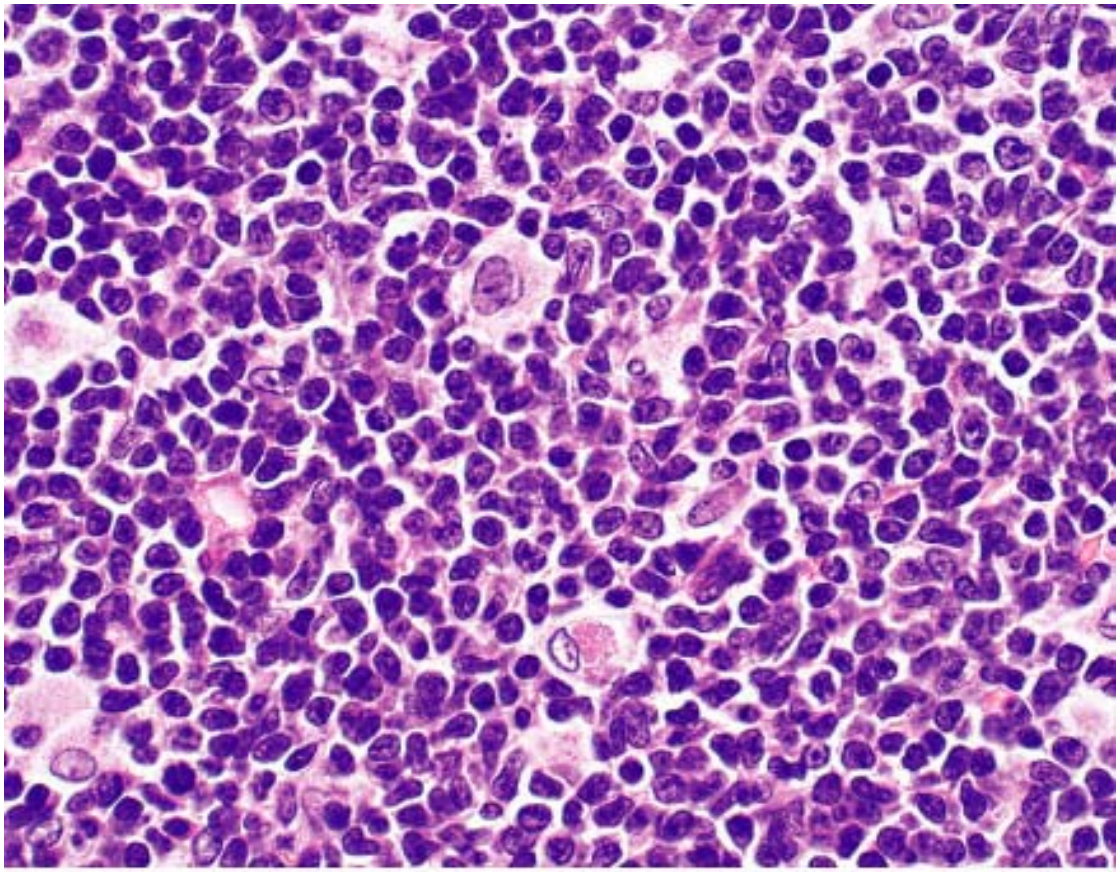
Mantle Cell Lymphoma

- Two commonly seen morphologic features of this lymphoma are
  - Hyalinized blood vesels
  - Scattering of epithelioid histiocytes resulting in a starry sky appearance
- Immunocytochemistry studies show that this is a distinct type of lymphoma having a features of lymphocytes of primary follicle or mantle zones of secondary follicles.
- Tumours cells are positive for Ig (IgM, IgD) B-cell associated antigen and CD5.
- Absence of CD23- is useful for distinguishing it from SLL and presence of CD5 is useful in D/D with follicular and marginal zone lymphoma.
- Cytogenetically-t(11;14), translocation is present 70% of cases which is detected by FISH. This translocation leads to overexpression of cyclin D1 protein which is constant and very specific feature of this lymphoma.
- This cyclin D1 protein promotes G1 to S phase progression during cell cycle
- This lymphoma may be difficult to distinguish from mantle zone hyperplasia and Castkleman's disaes. Determination of clonality of the infiltrate by ICC technique is important in this regard.
- In D/D with follicular lymphopma, clue is absence of centroblasts and immunoblasts in this lymphoma
- Blastic form of this lymphoma needs to be distinguished from lymphoblastic lymphoma.
- **C/F:** Painless LAD, with splenomegaly (50%). Prognosis- poor, median survival- 3-4 years.

Mantle cell lymphoma surrounding a small residual germinal center.



and that of small lymphocytic lymphoma.



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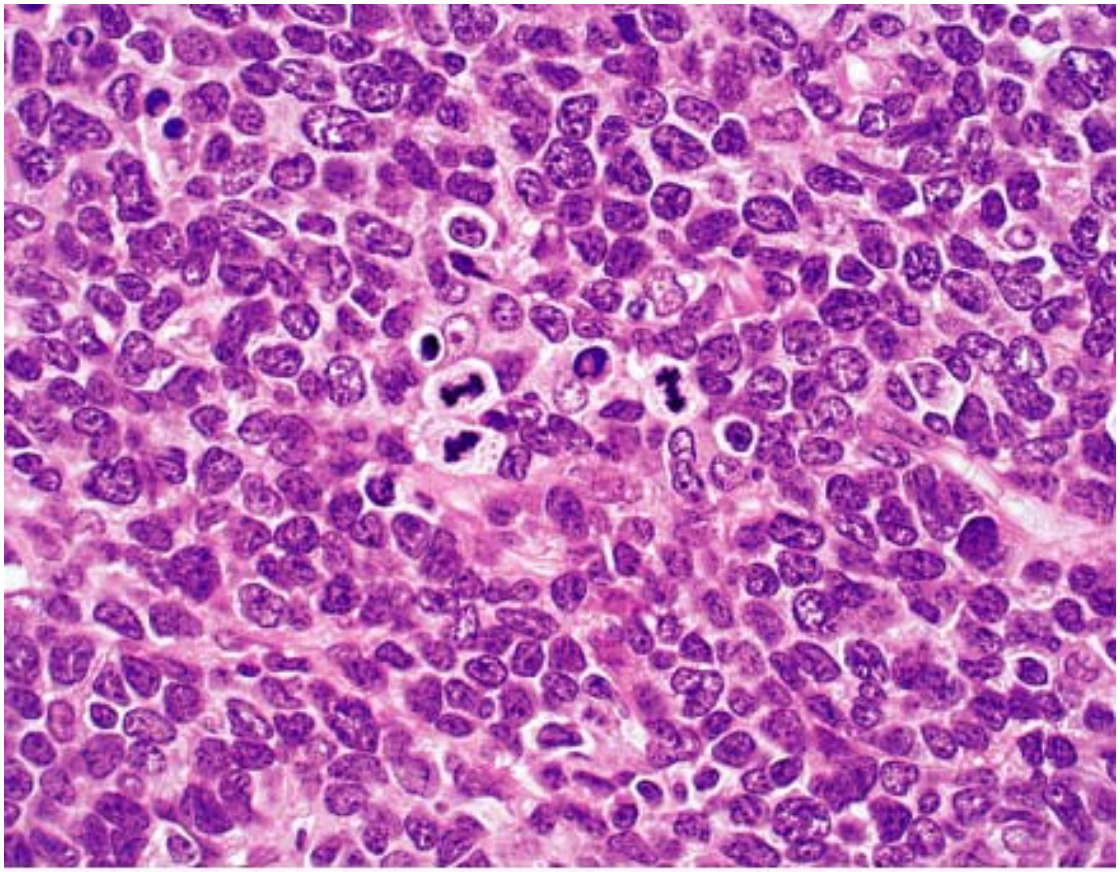
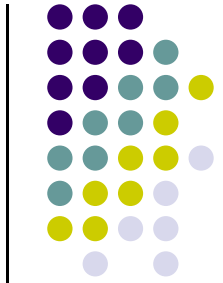
So-called “blastoid variant” of mantle cell lymphoma. A, **section showing high mitotic activity.**



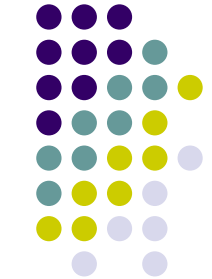
Marginal Zone B-cell Lymphoma



In this lymphoma, predominant tumour cell resemble normal marginal zone B-cells which represents a post germinal centre memory B-cell population.
Marginal Zone B-cell Lymphoma is the generic term used to designate a large family of low grade B-cell lymphoma such as

1. Monocytoid B-cell Lymphoma (L.node). Tumour cells are small to medium sized lymphocytes with round or slightly indented nuclei and relatively abundant clear, cytoplasm.
   - The pattern of involvement is predominantly sinusal and interfollicular, nodal form of this lymphoma is very rare disease (<2%) NHL
   - Clinically the disease is more common in women and often localized at presentation. Histologic transformation to large cell lymphoma has been documented in rare cases.

Marginal Zone B-cell Lymphoma

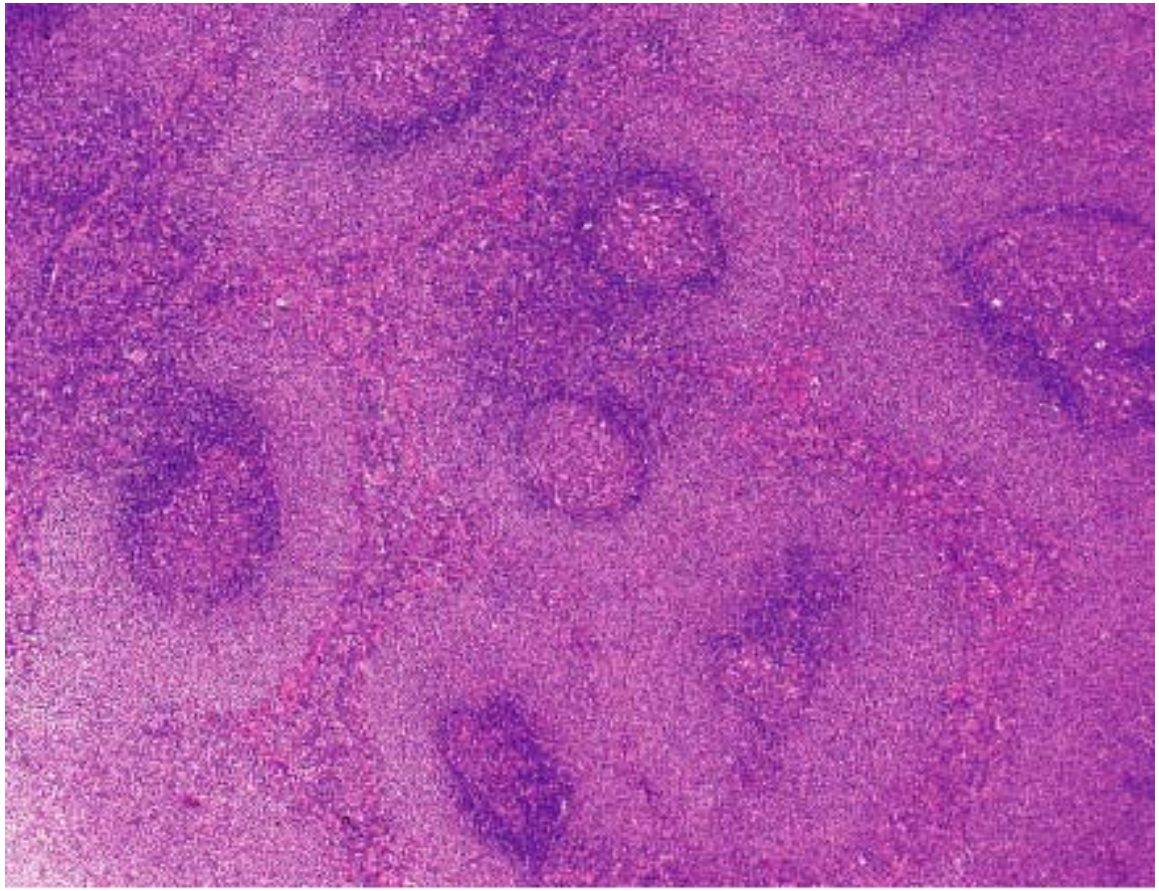


2. **Low grade lymphoma of Mucosa associated Lymphoid Tissue (MALT-Lymphoma)-** in this lymphoma, cell population includes – small round lymphocytes, monocytoid B-cells, cells with slightly irregular nuclei (centrocyte like) plasmacytoid cells, plasma cells and occasional large lymphoid cells.
   - Tumour is seen exranodal sites in realation to mucosa or glandular epithelia, such as GIT, salivary, lacrimal gland, lung, thyroid, bladder skin, it remains localised for long time and has tendency to relapse in the same site or other extranodal sites.
   - They often arise with in tissue involved by chronic inflammatory disorders of autoimmune or infectious etiology e.g., tumours arising from salivary gland in Sjogren disease, thyroid gland in Hashimoto thyroiditis and the stomach in Helicobacter gastritis, these tumour may regress if inciting agent is eradicated.
   - Immunohistochemically-there is no special cell marker that separate MALT lymphoma from others low grade B-cell lymphoma, however, as a group they are less likely to express CD5, CD25, and more likely to express CD11c. Trisomy 3 is frequent and some cases show t(11;18).

3. **Splenic Marginal Zone Lymphoma-** several cases of lymphoma involving the marginal zone of the spleen have been reported, some time is association with BM and peripheral blood involvement.

- Transformation to large cell lymphoma can occur in any forms of marginal zone B-cell lymphoma

Lymph node involvement by marginal zone B-cell lymphoma. There are numerous residual germinal centers.



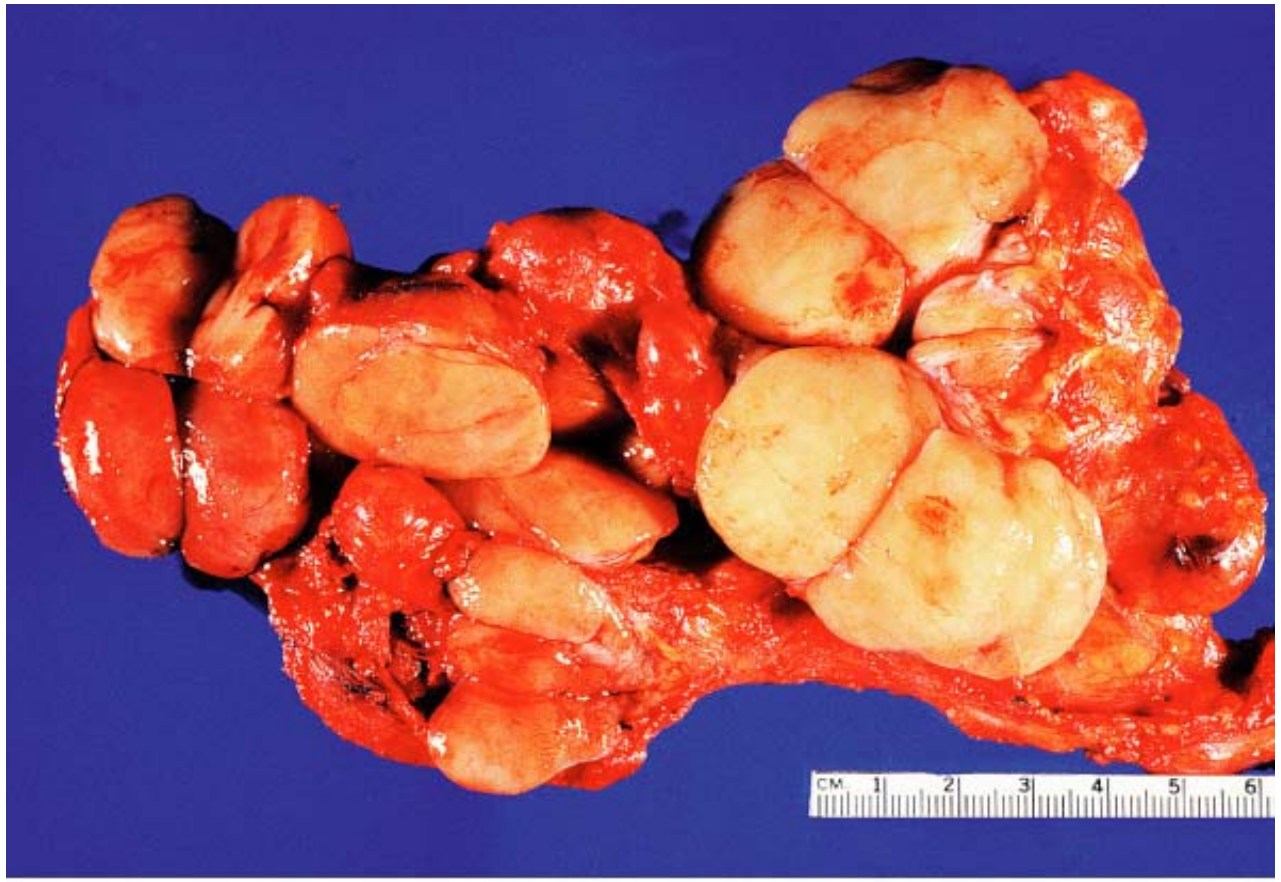
Diffuse Large B cell Lymphoma

- Most complex, heterogeneous of all NHL. This term replaces the old histiocytic lymphoma. It constitutes about 20% of all NHL and 60-70% of aggressive lymphoid neoplasms.

- Median age is about 60 years. However age range is wide and it also constitutes about 5% of childhood lymphoma.

- Morphologically- characterized by the large size of the cells, their vesicular nuclei, with prominent nucleoli with abundant cytoplasm.

Gross appearance of lymph nodes involved by non-Hodgkin's lymphoma of diffuse large B-cell type. The nodes are enlarged and show a homogeneous tan cut surface.



Diffuse Large B cell Lymphoma

- 40% cases shows extranodal sites; GIT, skin, skeletal system, liver, spleen. The involve nodes are usually markedly enlarged, homogenous with little or no necrosis. BM involvement usually occurs late. Rarely leukemic picture may emerge
- Progression- rapid, prognosis-poor if untreated, but shows excellent response to chemotherapy

- 50-60% of large cell lymphoma has B-cell marker
- 5-15% has T-cell marker.
- A few have true histiocytic features
- And if no marker at all k.a. Null Lymphoma
- Microscopically- pattern – diffuse, mitosis- are numerous

Diffuse Large B cell Lymphoma

Subclassification depending upon type of large cell present

- **Centroblastic-** it is a diffuse counterpart of the nodular form of follicular lymphoma.

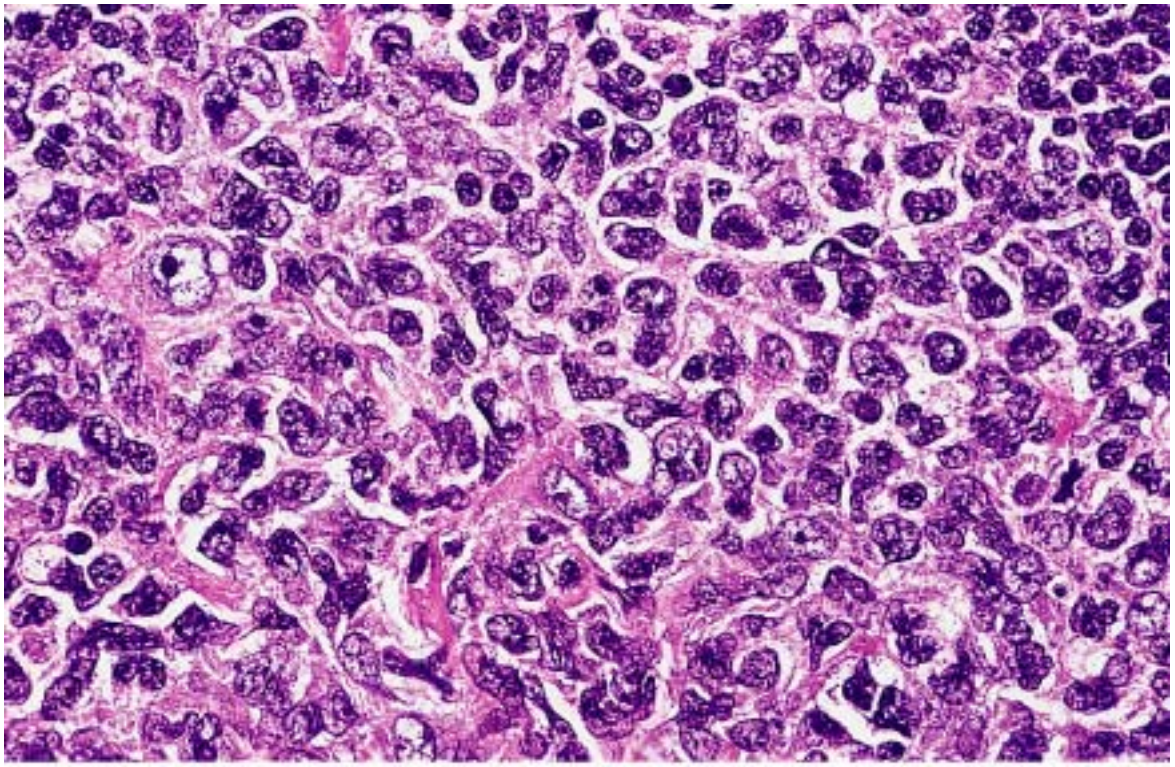
  Composed of an admixture of varying proportion of cleaved and non cleaved large cells. When non cleaved cells predominate, distinction with immunoblastic variant becomes difficult.

  The main morphologic difference are –lighter staining, less pyroninophilic cytoplasm, the more peripheral location of the nucleoli, absence of plasmocytoid differentiation, presence of scattered small and large cleaved cells.

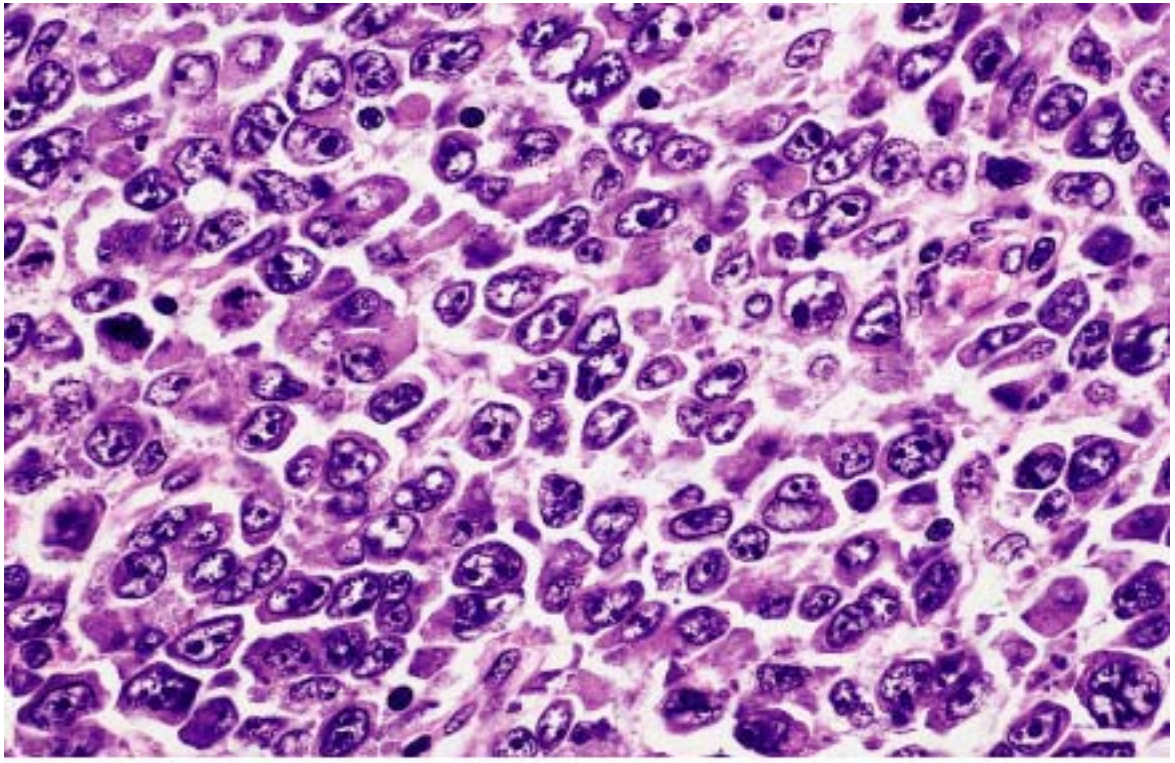
- **Immunoblastic-** tumour cells have appearance of an immunoblast, large vesicular nucleus with prominent central nucleolus and thick nuclear membrane and deeply amphophilic and pyroninophilic; cytoplasm with a distinct nuclear hof, some of the cells are binucleated, multinucleated and may resemble R.S. cell and other acquire plasmocytoid appearance.

  This type of lymphoma is associated or arising on the basis of mutual immunodeficiency, Immunosuppression and immunoproliferative states

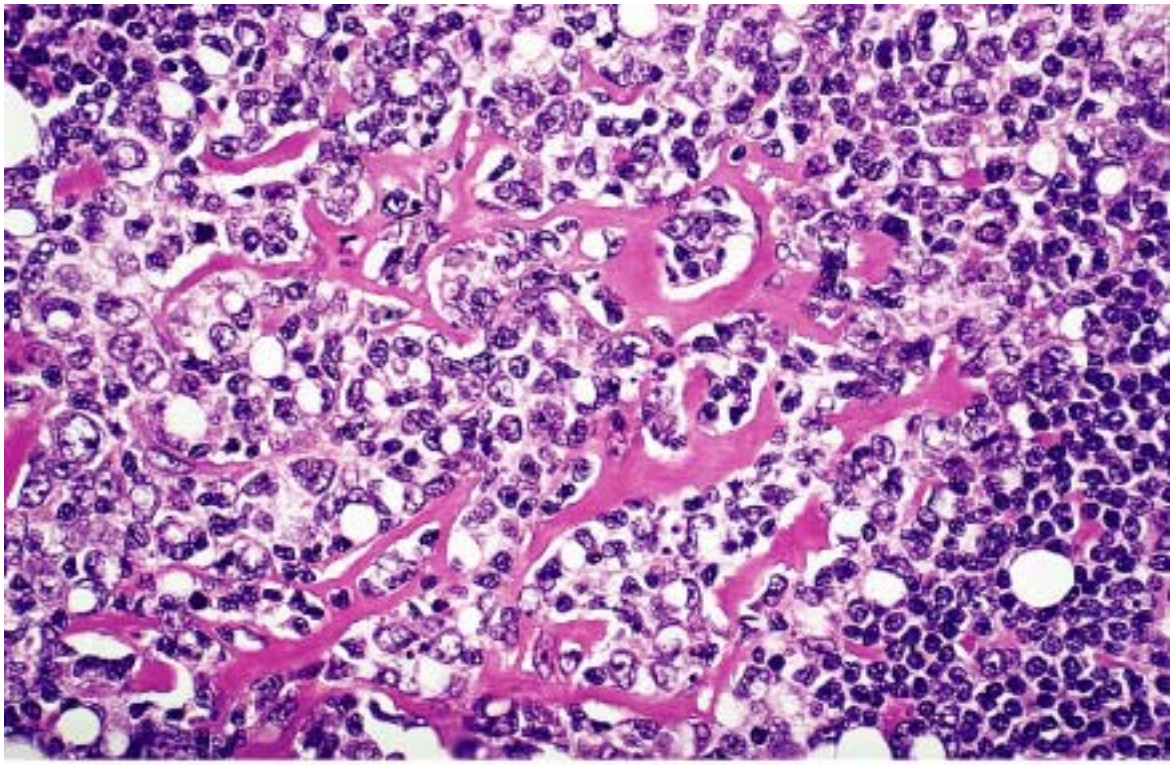
High-power views of diffuse large B-cell lymphoma of large cleaved type.



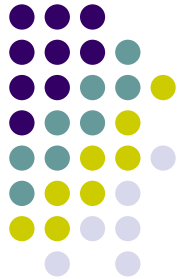
High-power views of diffuse large B-cell lymphoma of immunoblastic type.



Marked sclerosis and hyalinization in diffuse large B-cell lymphoma.

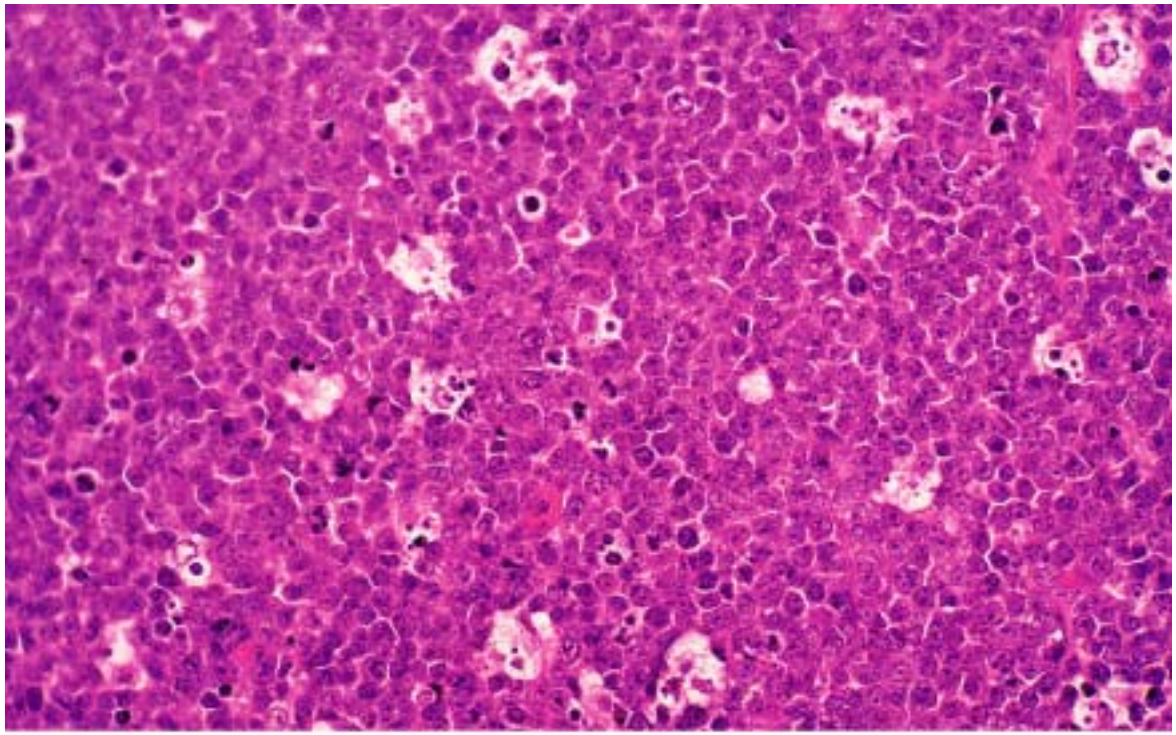


Burkitt's Lymphoma



- High grade malignant lymphoma composed of germinal centre B cell which can present in 3 clinical settings.
  - Endemic-occurs in Aferica, most common form of childhood malignancy in this area. Pts. Present with jaw and orbital lesions.
  - Sporadic- affects mainly children and adolescents seen through out the world, greater tendency for involvement of the abdominal cavity.
  - Immunodeficiency associated: seen in cases with HIV infection.
- In all three forms peripheral lymphoadenopathy is rare. Bone marrow involvement is common in later stage.
- **M/E-** seen in diffuse form, however, earlier stage shows involvement of germinal centres. Tumour cells are small (10-25µm) & round; nuclei- round, oval, and have several basophilic prominent nucleoli, chromatin- coarse and nuclear membrane is thick. Cytoplasm- it is amphophilic and strongly pyroninophilic, mitosis are numerous and a prominent starry sky pattern.
- E/M- there is abundant ribosomes, glycogen, particles and presence of nuclear packets or projections.

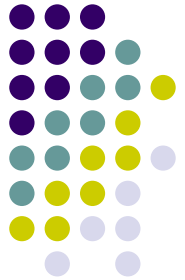
Burkitt’s lymphoma with characteristic starry sky appearance.



Burkitt's Lymphoma

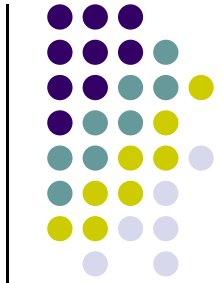
- **Morphological variants: two mainly**
  - Plasmacytoid differentiation- common in HIV, basophilic cytoplasm containing Ig and a single central nucleolus.
  - Atypical/pleomorphic form- cell size larger, distinct pleomorphism is present, most of the cells have a well defined rim of cytoplasm nucleus contain a large eosinophilic nucleolus, binucleated/multinucleated cells are common. Phagocytosis of nuclear debris by reactive histiocytes is common, resulting in a starry sky appearance.

- Immunohistochemically – all cases of this lymphoma are B-cell lineage
- Cytogenetically- 80% shows t(8;14) translocation, which results in the juxtaposition of the myc gene, so there is deregulation of myc gene expression, and ↑ed cell proliferation



Thank You

Modified Ann Arbor Staging



- **Stage I** Involvement of a single lymph node region
- **Stage II** Involvement of ≥2 lymph node regions on the same side of the diaphragm
- **Stage III** Involvement of lymph node regions on both sides of the diaphragm
- **Stage IV** Multifocal involvement of ≥1 extralymphatic sites ± associated lymph nodes or isolated extralymphatic organ involvement with distant nodal involvement