LYMPHORETICULAR SYSTEM

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LYMPHOID ORGANS

- **CENTRAL/PRIMARY**

Where new lymphocytes are produced

- Bone marrow
- Thymus

- **PERIPHERAL/SECONDARY**

Where lymphocytes respond to antigens

- Lymph nodes
- Spleen
- Tonsils
- Mucosa/skin associated lymphoid tissue (MALT)

Spleen

- **Anatomy**

➢ Weight : 150gms,

Histologically shows white pulp & red pulp

- **Functions of spleen-**

➢ Removal of unwanted elements from blood

➢ Major secondary organ of immune system

➢ Site of extramedullary haematopoesis

Rarely a primary site of disease

Involved in all systemic inflammation, generalized haematopoietic disorders & metabolic disorders.

Splenic enlargement is the major manifestation.

Splenomegaly (Splenic enlargement)

- Important diagnostic clue to an underlying disorder
- Itself can cause problems
- Dragging sensation in left upper quadrant esp. discomfort after eating

Clinical degree of enlargement

Mild enlargement (up to 5 cm)

CVC congestive spleen, acute malaria, typhoid fever

Moderate enlargement (up to umbilicus)

Hepatitis, cirrhosis, lymphoma, hemolytic anemia, amyloidosis

Severe enlargement (below umbilicus)

Chronic myeloproliferative disorder, storage disorder, chronic malaria, kala azar (leishmaniasis), Hairy cell leukemia, Prolymphocytic leukemia

Causes of splenomegaly

1. Infections – Infectious mononuclosis, tuberculosis, typhoid fever, brucellosis, malaria, leishmaniasis
2. Congestive states related to portal hypertension – cirrhosis, portal or splenic vein thrombosis, cardiac failure
3. Lymphohaematogenous disorders – HL, NHL, multiple myeloma, HA,TTP
4. Immunologic conditions – RA, SLE
5. Storage disorders – Gaucher's disease, Niemann pick's disease
6. Miscellaneous – Amyloidosis, Primary neoplasms & cysts, secondary neoplasms, Neoplasms

Neoplasia

Neoplastic involvement rare except in tumours of lymphoreticular system (Splenic lymphoma with villous lymphocytes)

Benign tumours: fibroma, osteomas, chondroma, lymphangioma, hemangioma

Metastases from malignancies of lung, breast, prostate, colon & stomach

Hypersplenism

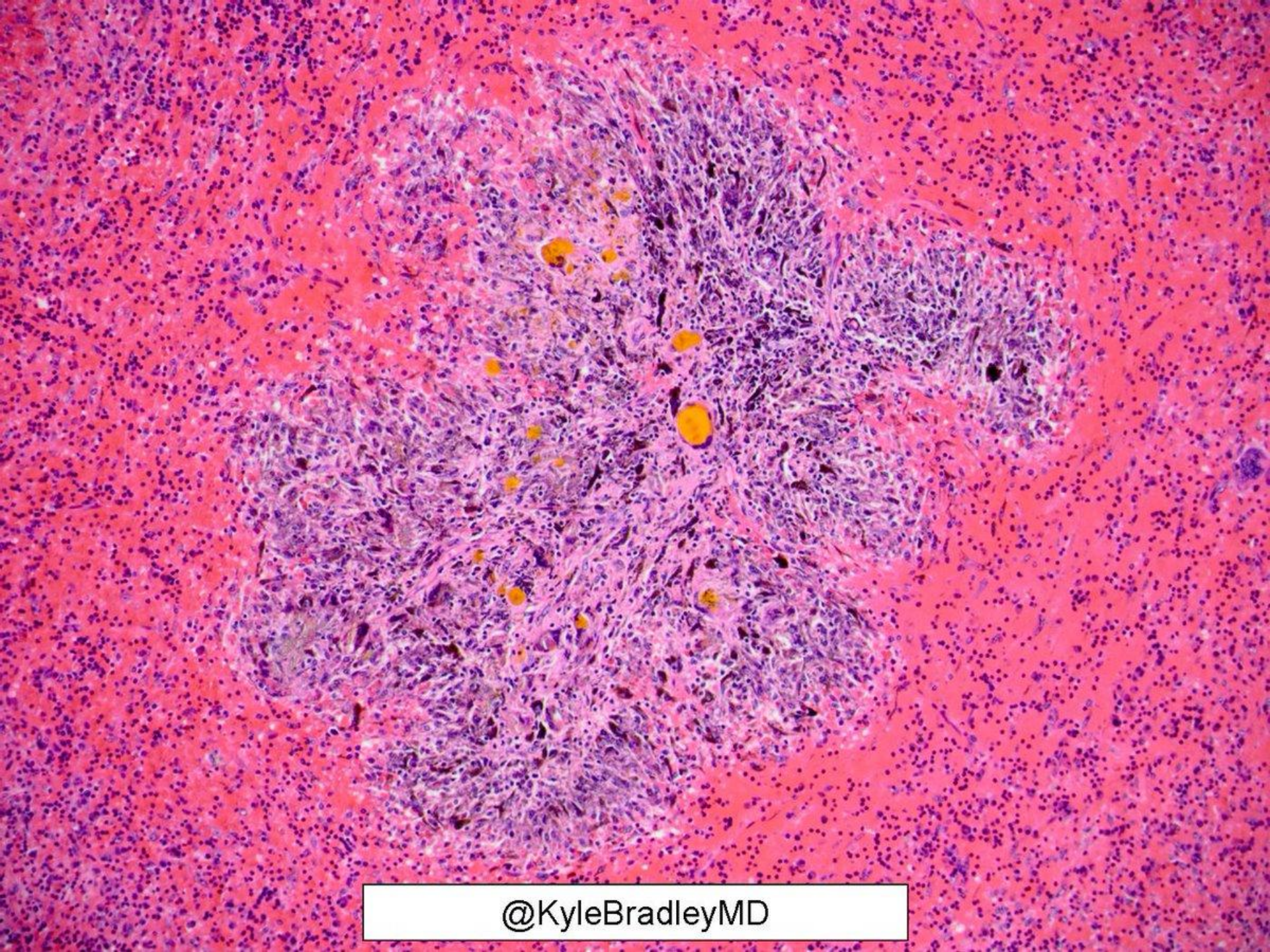
Splenomegaly, Pancytopenia, Normal bone marrow and correction of pancytopenia after splenectomy.

Congestive splenomegaly (splenic enlargement in CVC)

Grossly : Spleen enlarged & firm. Capsule thickened & fibrous

Microscopically : Congested red pulp, foci of recent & old hemorrhages

Gamna-Gandy bodies – foci of fibrosis along with deposition of iron & calcium salts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Lymph node

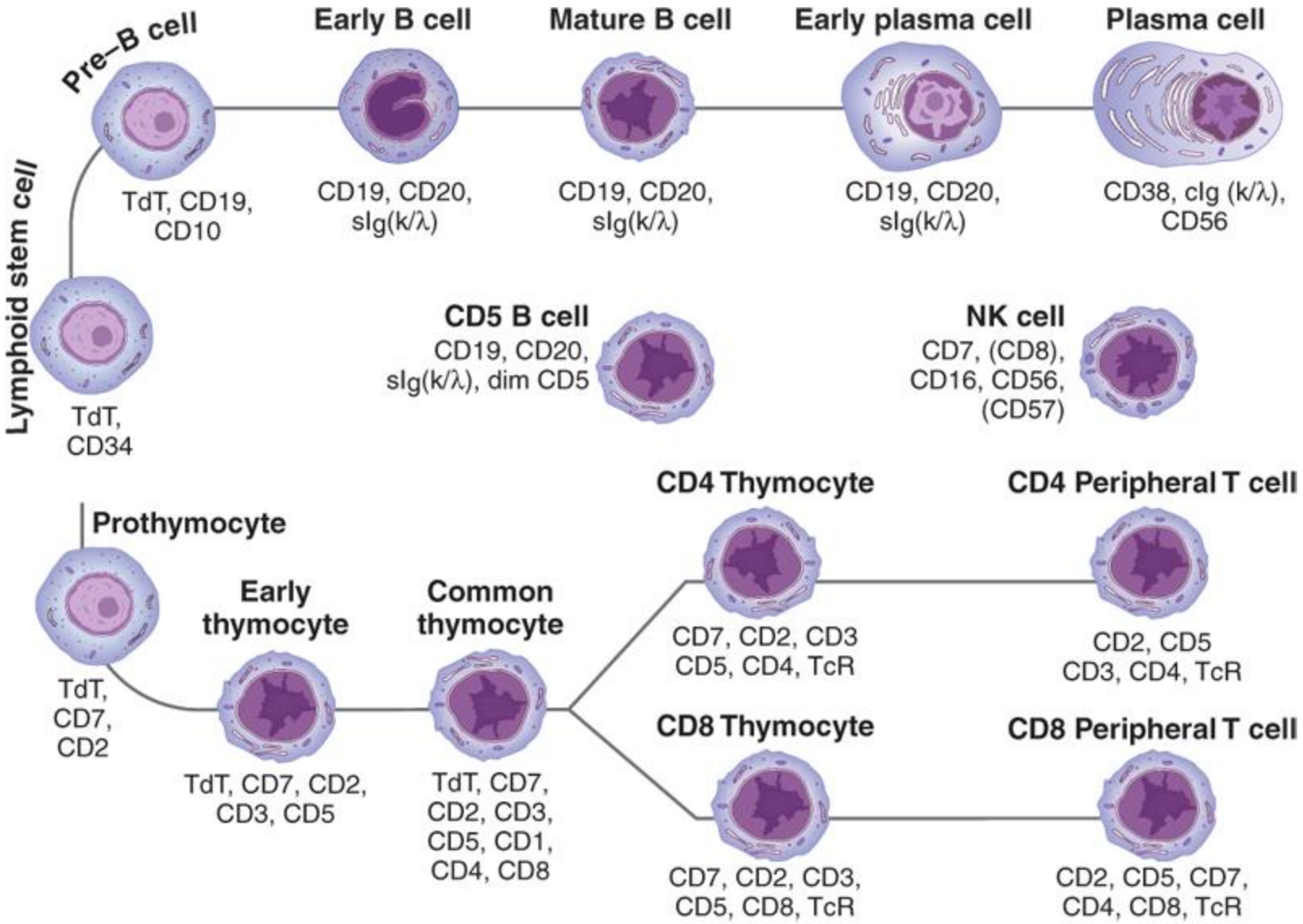
Lymph nodes are most widely distributed & easily accessible component of lymphoid tissue . Hence are frequently examined for diagnosis of Lymphoreticular disorders.

Functions of LN

- To mount immune response in the body
- To perform the function of active phagocytosis for particulate matter

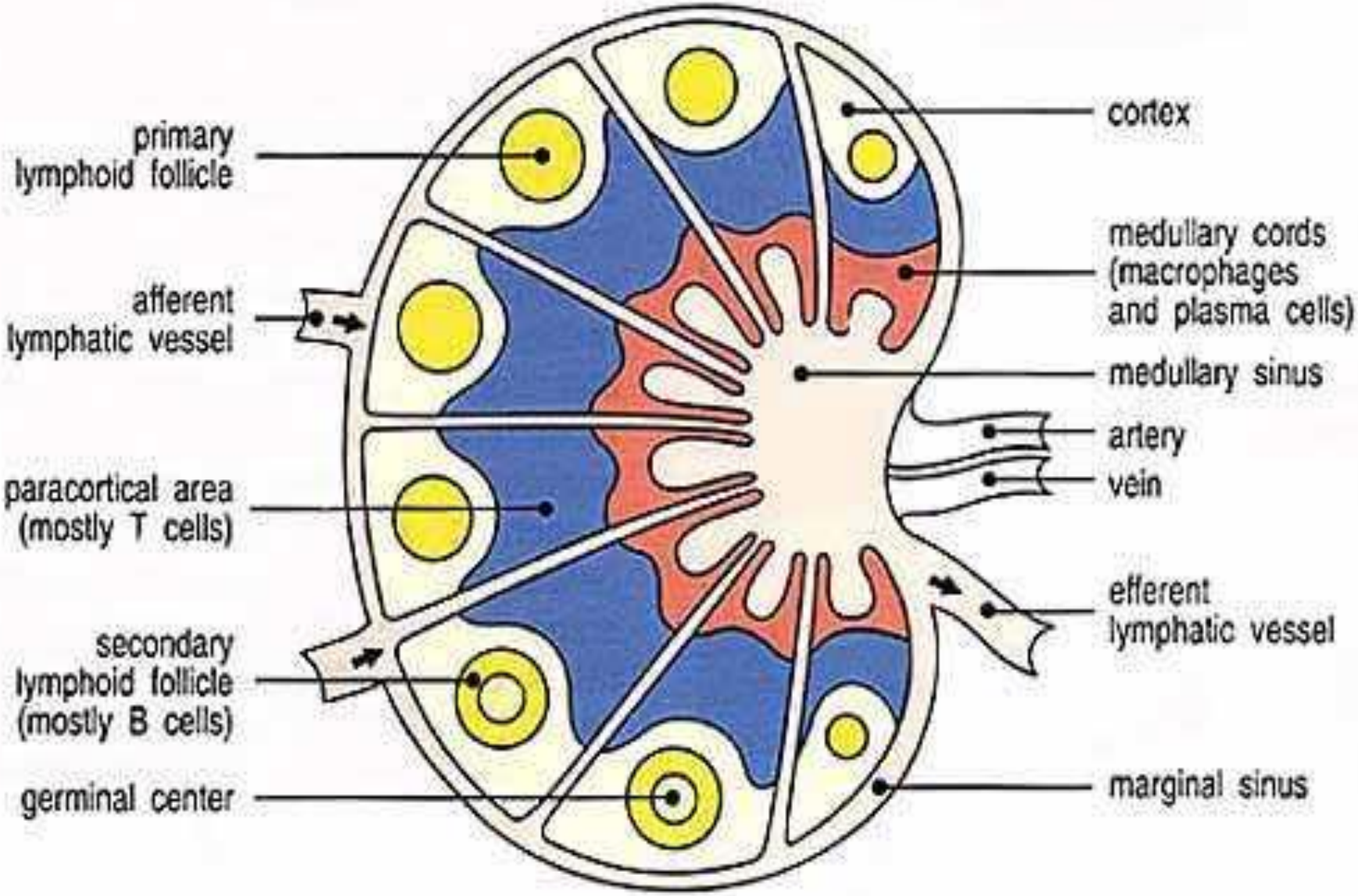
LNs are constantly responding to stimuli.

LN s in adult are almost never normal & usually bear the scar of previous events.



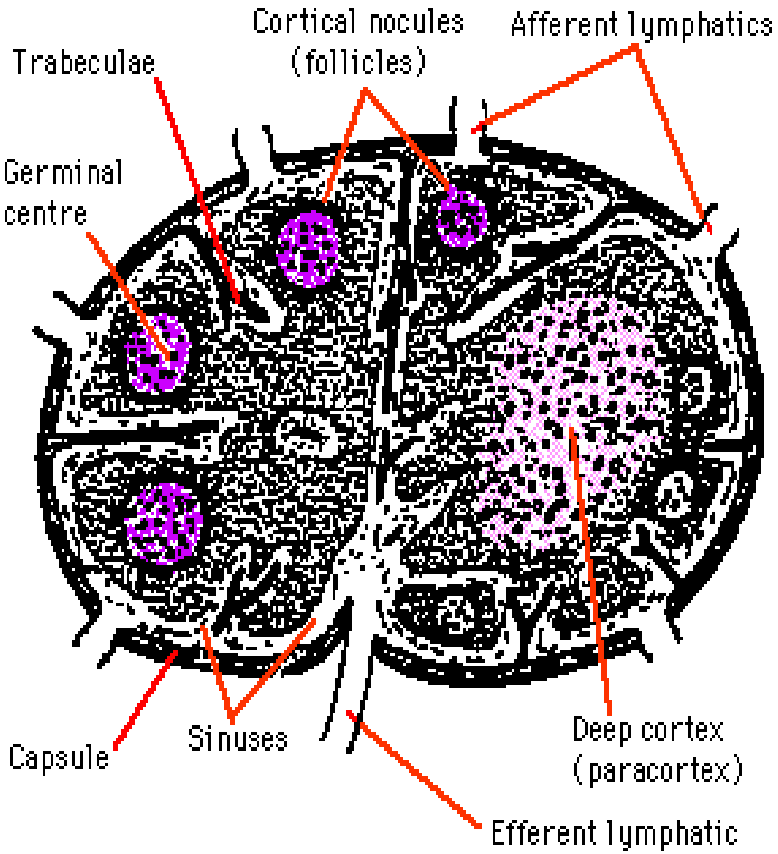
Source: R.S. Hillman, K.A. Ault, M. Leporrier, H.M. Rinder: Hematology in Clinical Practice, Fifth Edition, www.hemonc.mhmedical.com

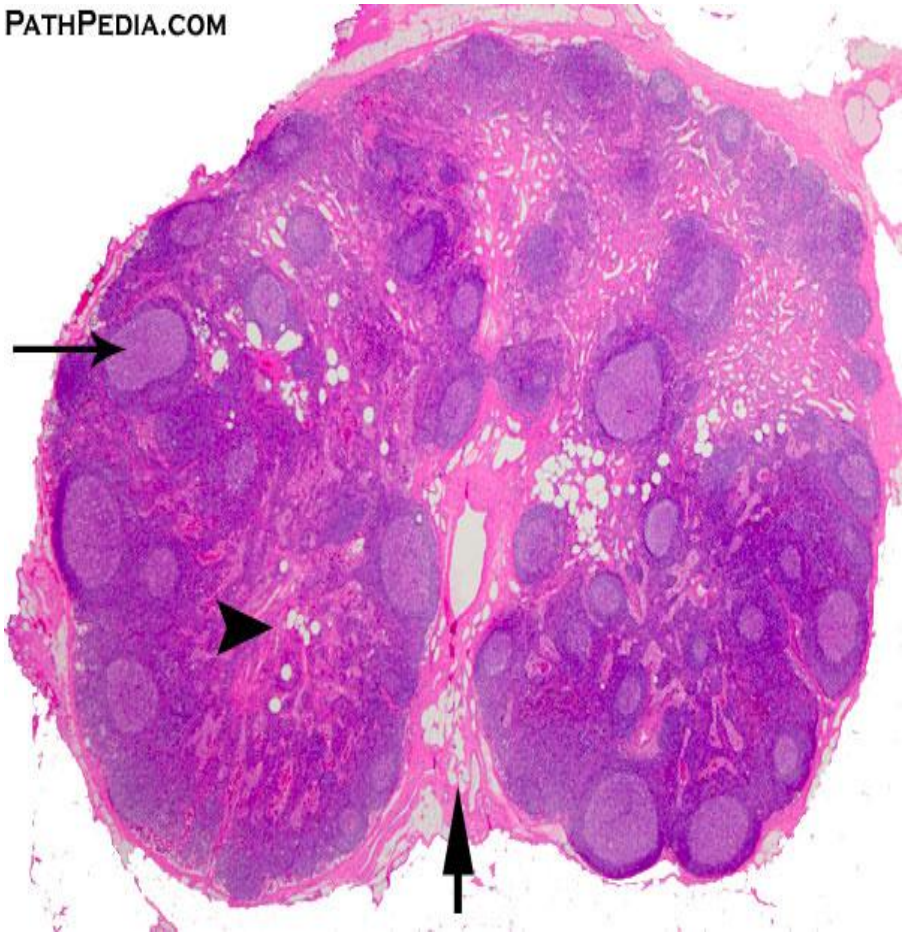
The lymph node



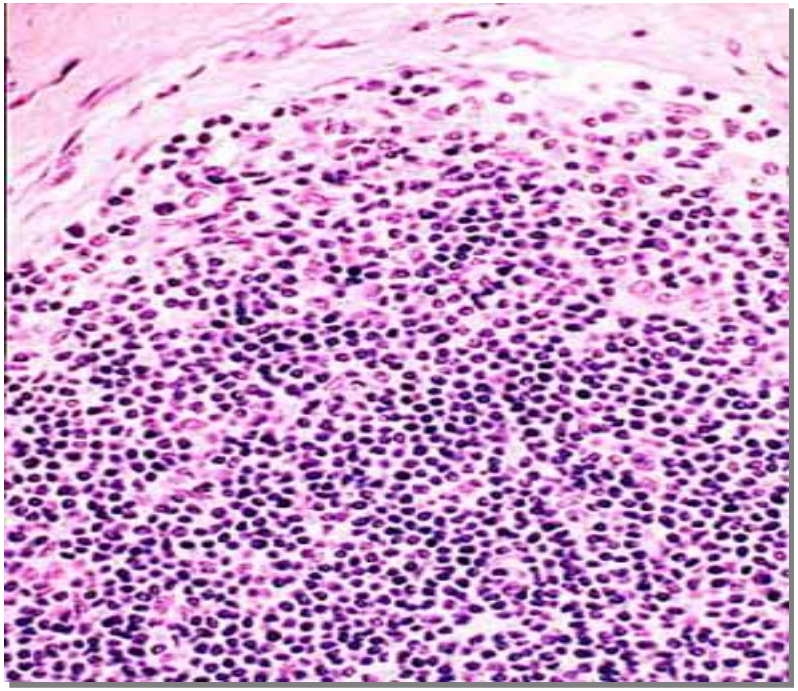
Lymph node

- **Normal structure**

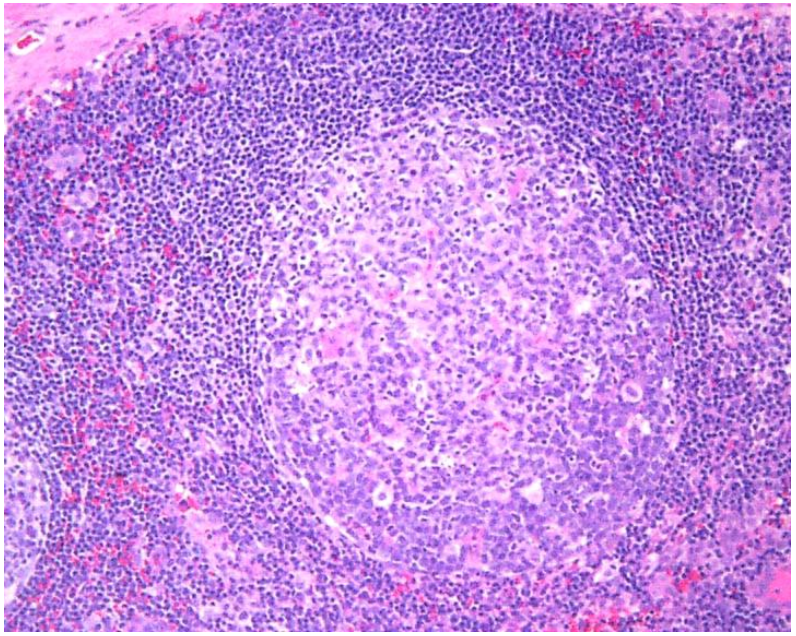




- PRIMARY FOLLICLES
  - In the absence of immune stimulation



- SECONDARY FOLLICLES OR GERMINAL CENTERS
  - In the presence of immune stimulation.



- **Disorders of white cells**

1.Proliferative : Reactive (more common)

Neoplastic (more important)

2.Leucopenias

Reactive lymphadenitis –

LNs undergo reactive changes in response to wide variety of stimuli

microbial infection, drugs, injury, immune reactions

Reactive lymphadenitis : **Primary inflammatory**

Lymphadenopathy : **Primary immune reactions**

INFECTIONS

- SPECIFIC

i. Bacterial: TB, syphilis, brucellosis

ii. Viral : Infectious mononucleosis, PGL OF HIV, LGV

iii. Fungal : Histoplasmosis, blastomycosis, coccidomycosis

iv. Parasitic : Filariasis, toxoplasmosis

- NONSPECIFIC

i. Acute

ii. Chronic

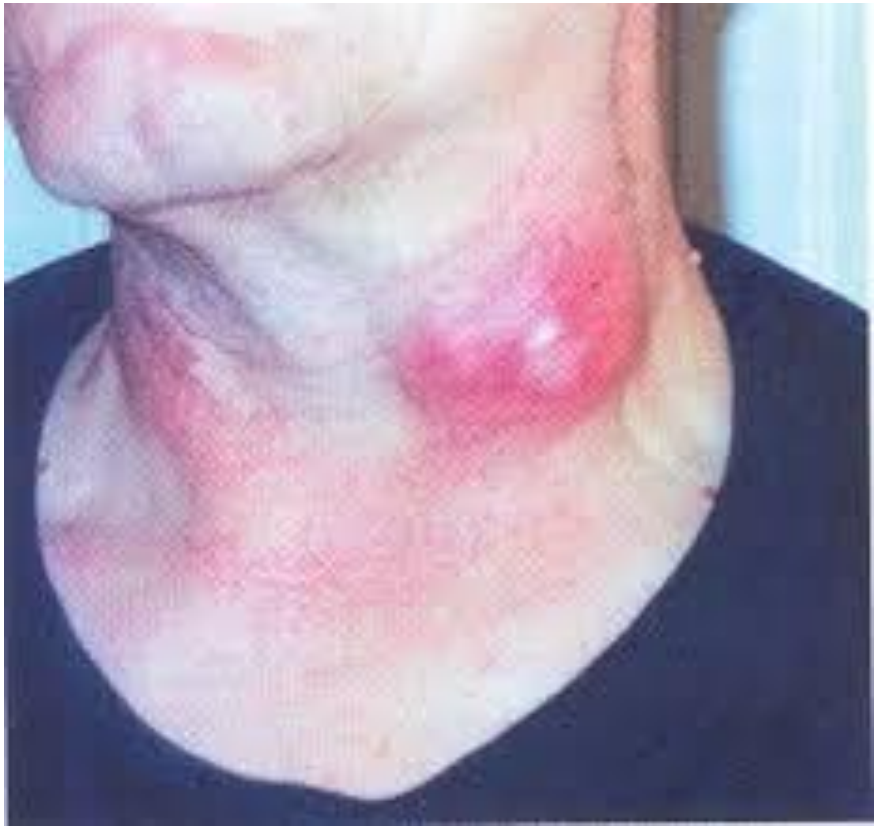
ACUTE NONSPECIFIC LYMPHADENITIS

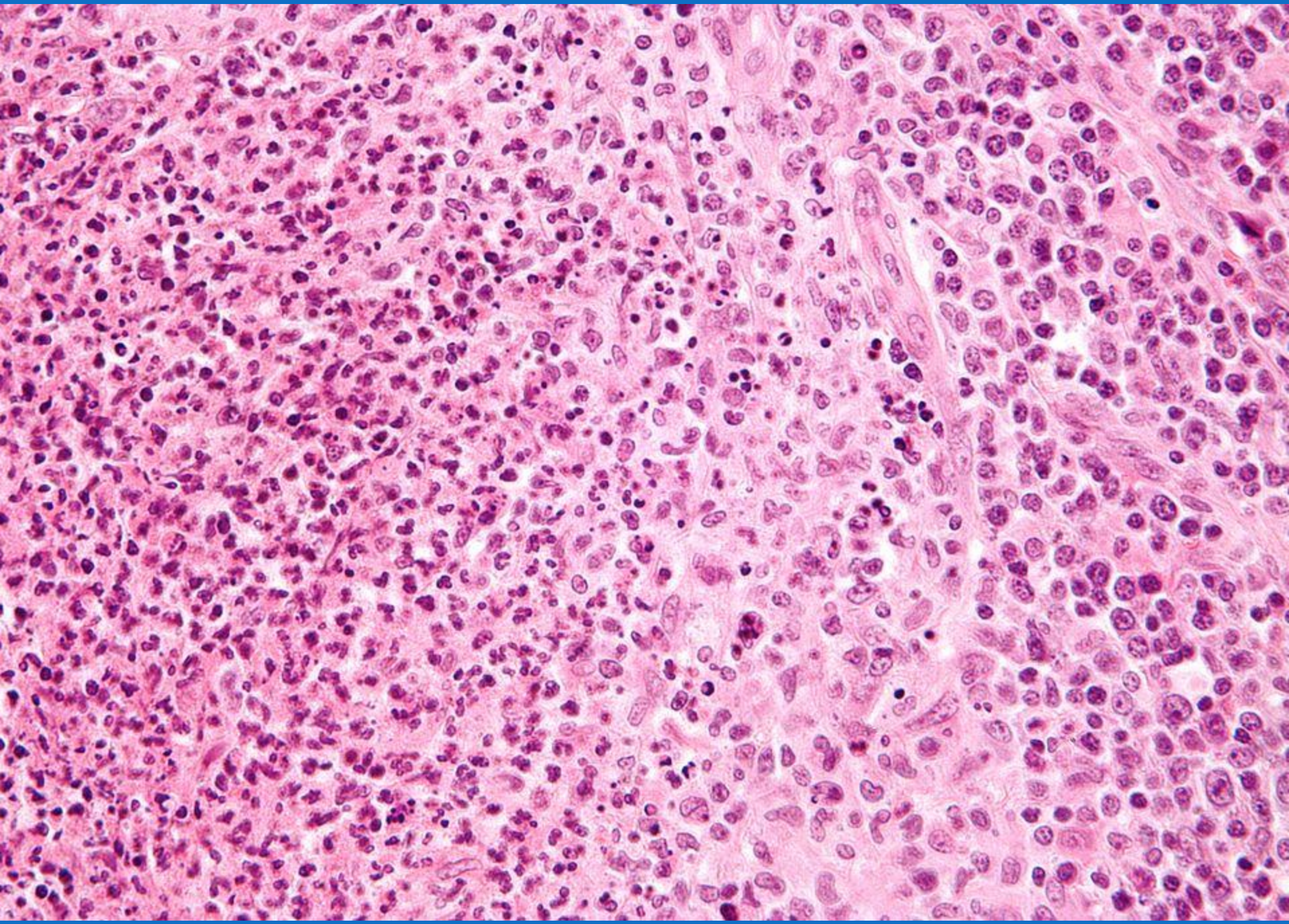
Cervical LN : Infections of teeth or tonsils
Axillary or Inguinal LN : Infections in extremities
Mesentic lymph nodes : Acute appendicitis
Generalized LN : Children in bacteremia & systemic viral infections

C/F : Enlarged LN - because of cellular infiltration & edema
Tender - because of distension of capsule
With extensive abscess formation they become fluctuant draining sinuses may be formed

Grossly : Nodes are swollen, red & engorged

HPE : Prominent germinal center
Tingible body macrophages (Macrophages with particulate debris)
Areas of necrosis- center of follicle
Numerous neutrophils in the follicles and sinuses





- **Chronic Nonspecific Lymphadenitis**

  - Enlarged & non tender nodes
  - Inguinal & axillary nodes

- **REACTIVE HYPERPLASIAS**

  PROMINENT PATTERNS

1. Follicular hyperplasia
2. Paracortical hyperplasia
3. Sinus histiocytosis

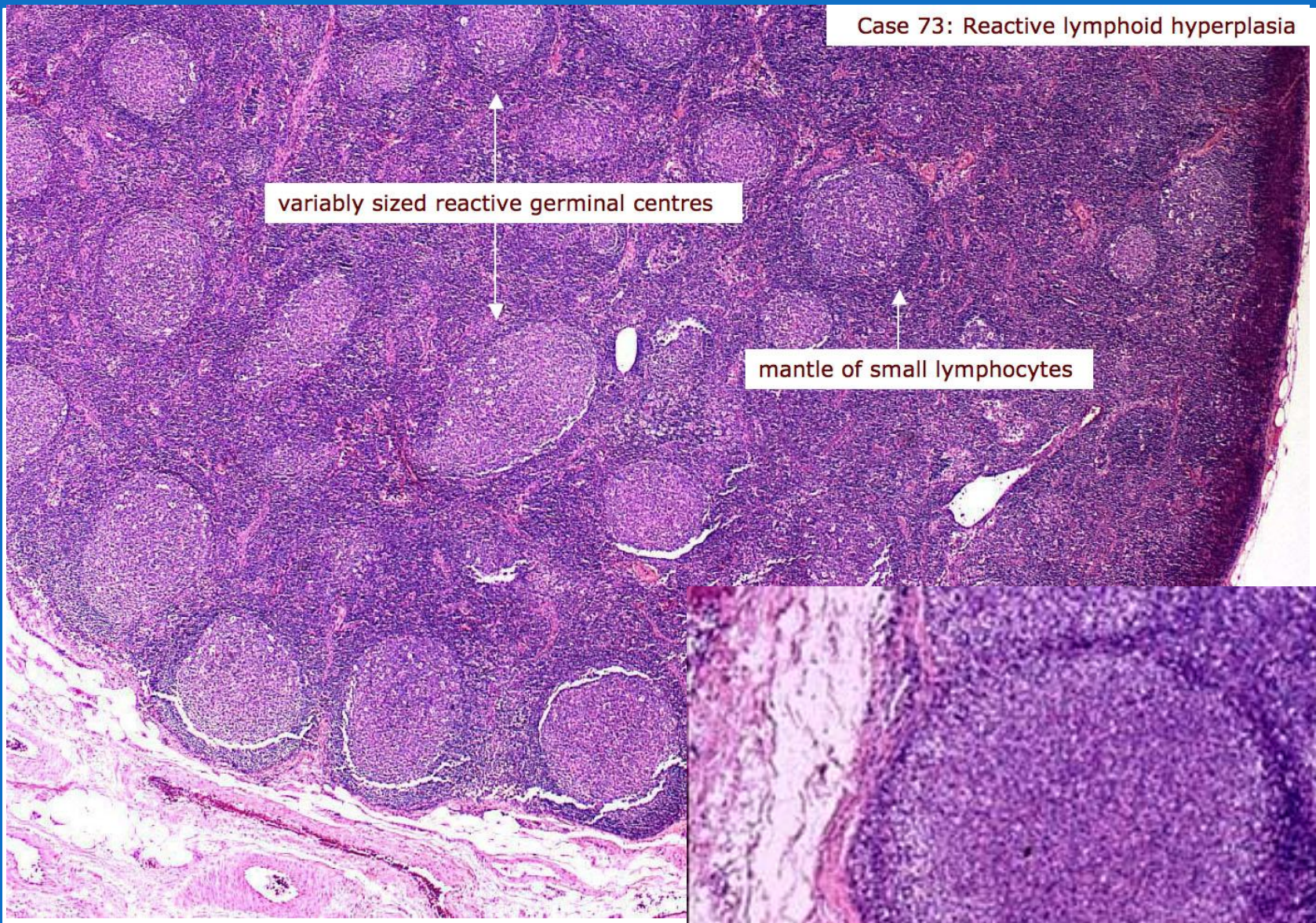
A. Follicular Hyperplasia

- Increase in no and size of germinal centres (B cell area), may involve paracortex and medullary areas
- Plasma cells, histiocytes & neutrophils in the sinuses
- Hyperplasia of mononuclear phagocytic cells lining sinuses

Seen in-

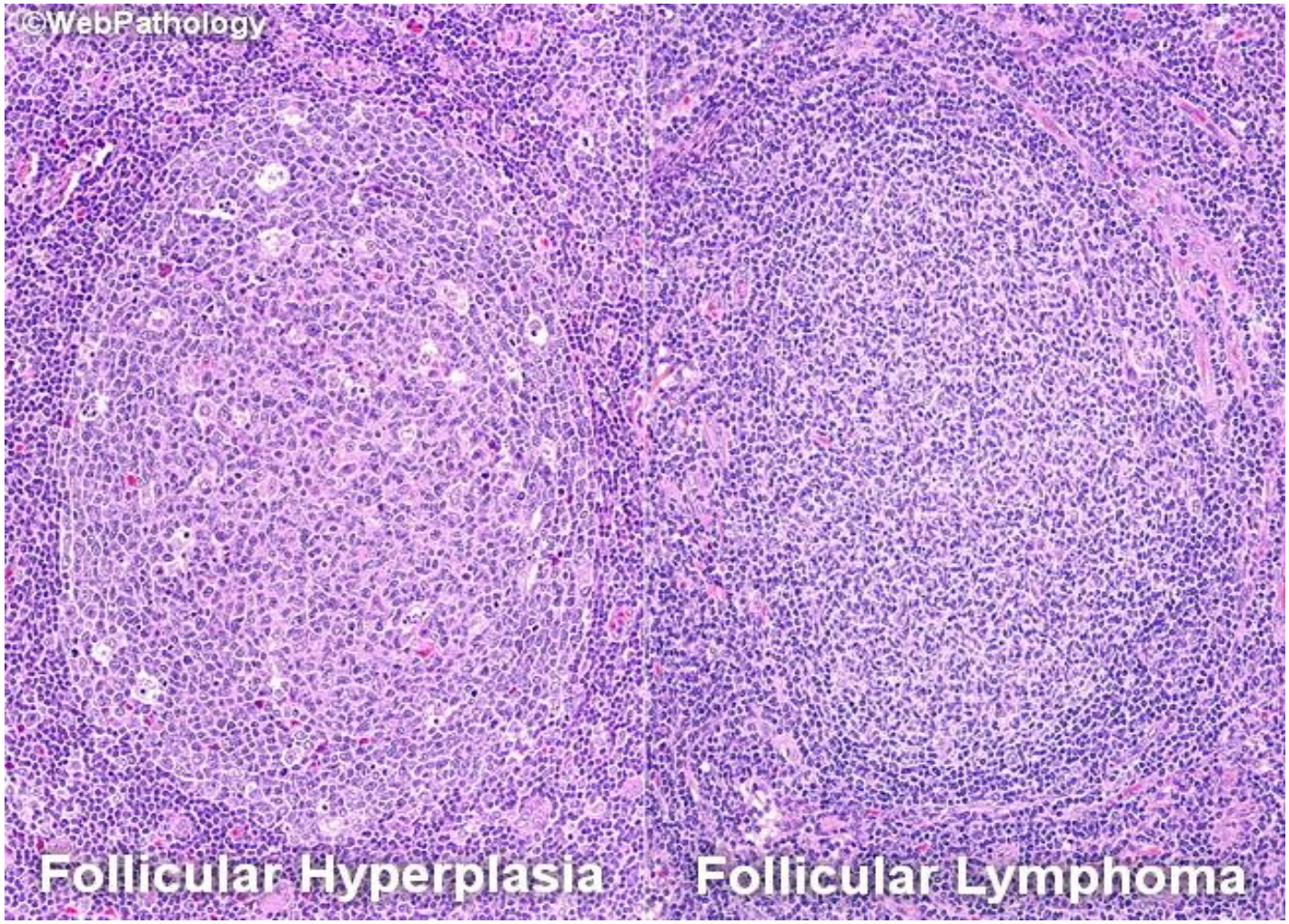
- collagen vascular disorders (RA)
- Systemic toxoplasmosis

Case 73: Reactive lymphoid hyperplasia



Confused with follicular lymphoma

1. Preservation of lymphoid architecture
2. Marked variation in size & shape of lymphoid follicle
3. Presence of frequent mitotic fig, phagocytic macrophages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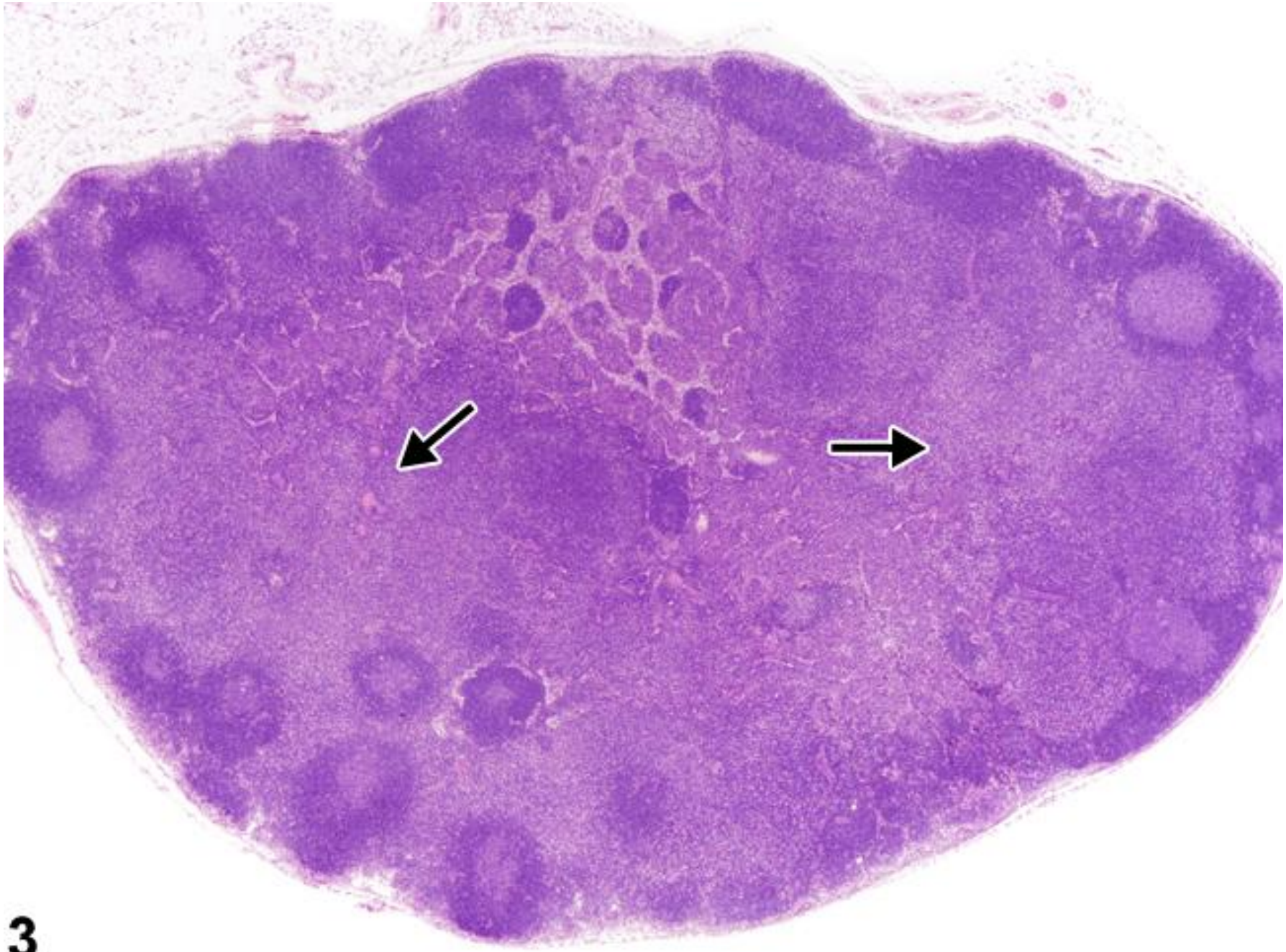
Follicular Hyperplasia
Follicular Lymphoma

B. Paracortical Hyperplasia

- Increase in interfollicular / paracortex elements (T cell area)
- small compressed follicles
- Increased subcortical infiltrates
- hypertrophy of sinusoidal & vascular endothelial cells, mixed cellular infiltrate

Seen in

- Viral infections (low grade) – Infectious Mononucleosis
- Drug reaction (Dilantin)
- SLE



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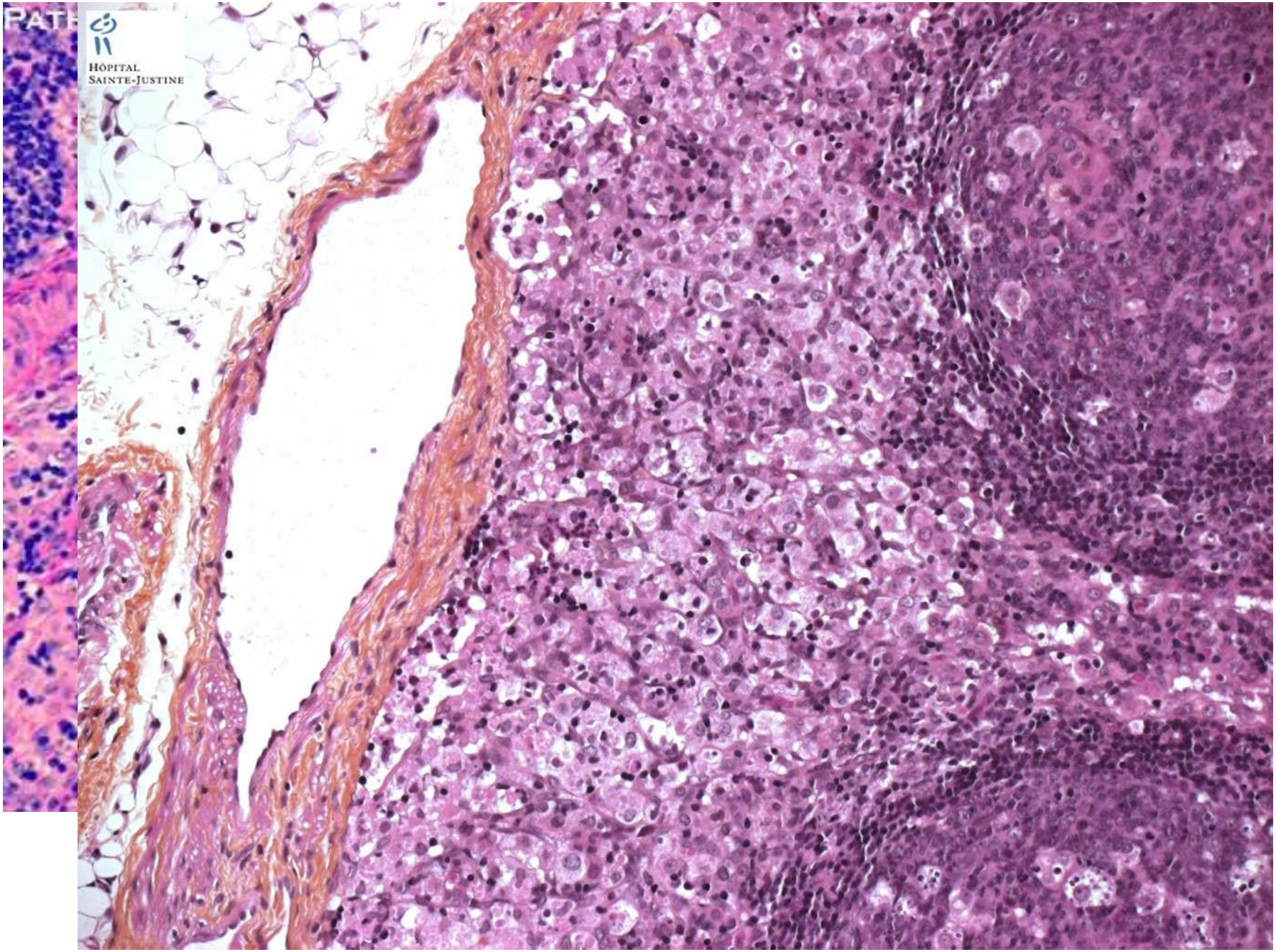
C. Sinus Histiocytosis

- Expansion of medullary sinuses due to histiocytes
- Selective proliferation of histiocytes
- Sinusoid lining endothelial cells markedly hypertrophied

Seen in-

- Malignancy adjacent to lymph nodes
- Chronic Infections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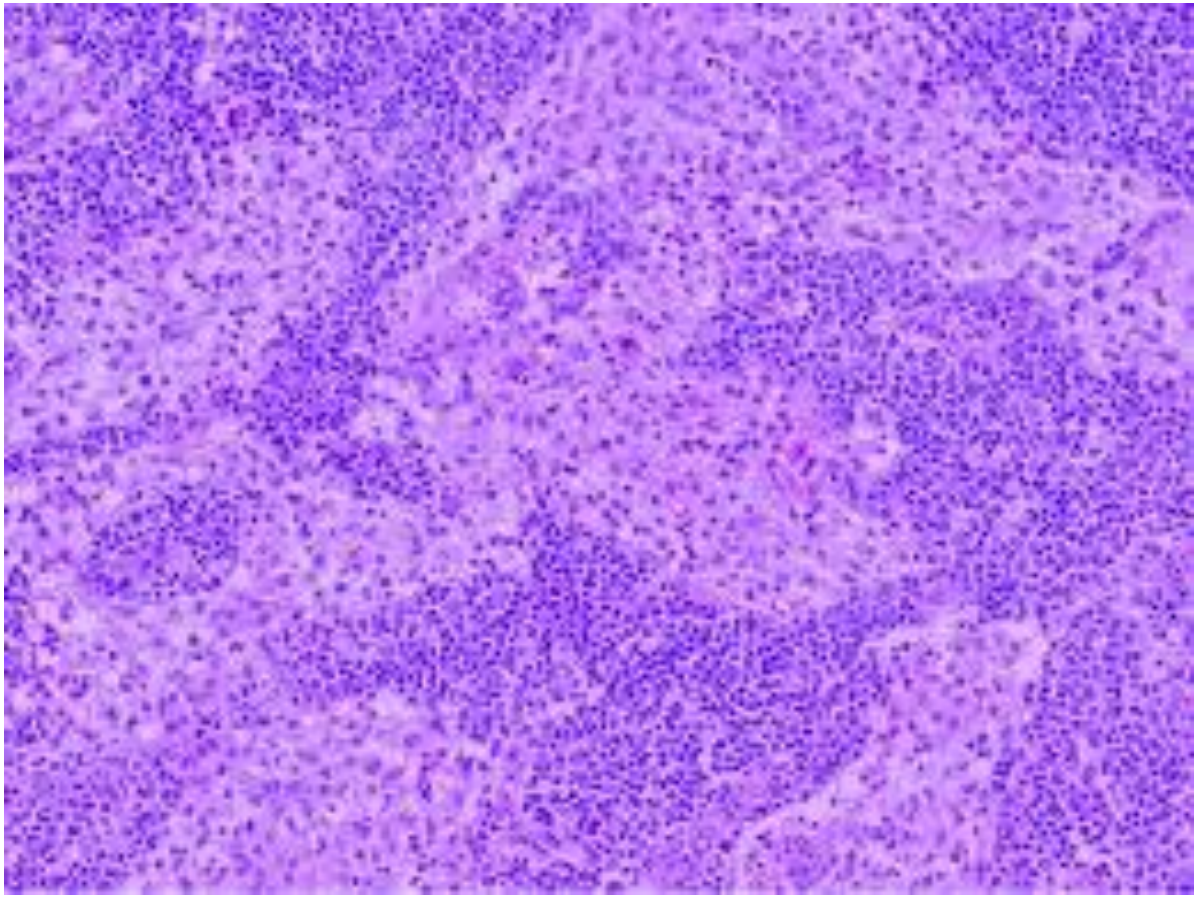
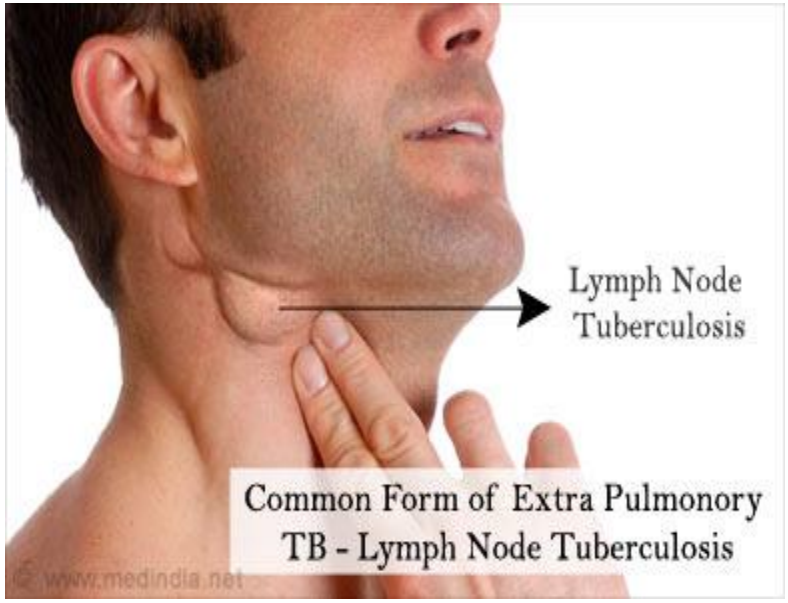
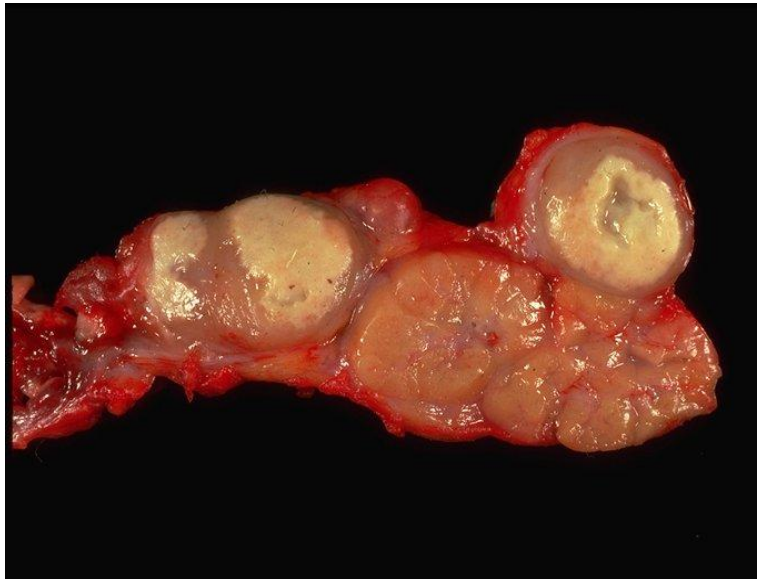


Tuberculous lymphadenitis





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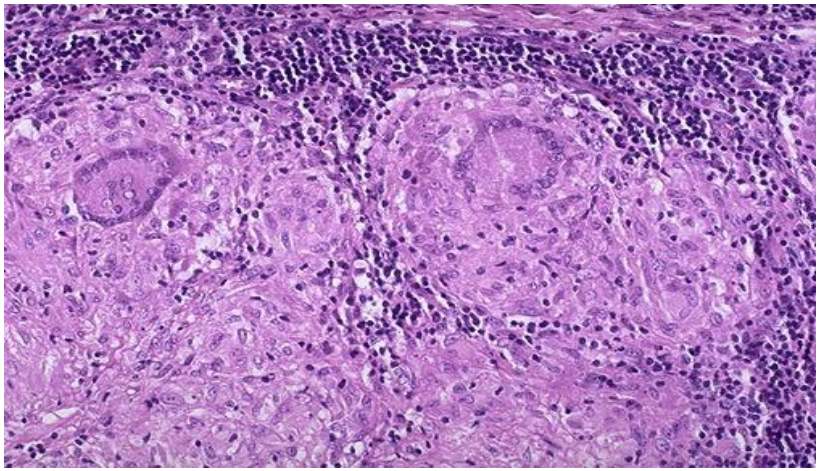
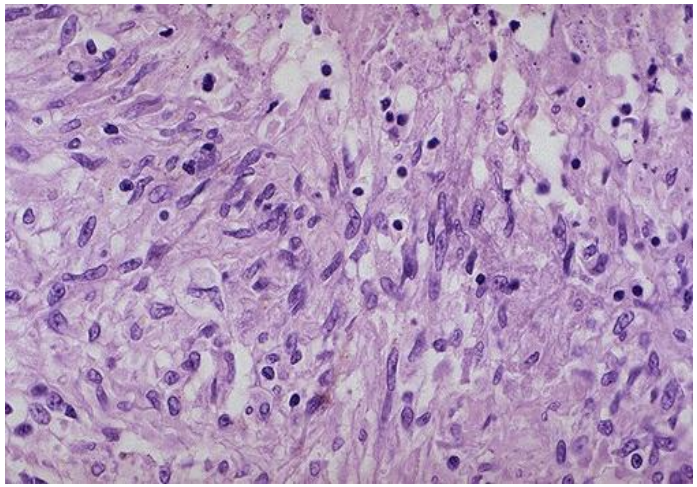
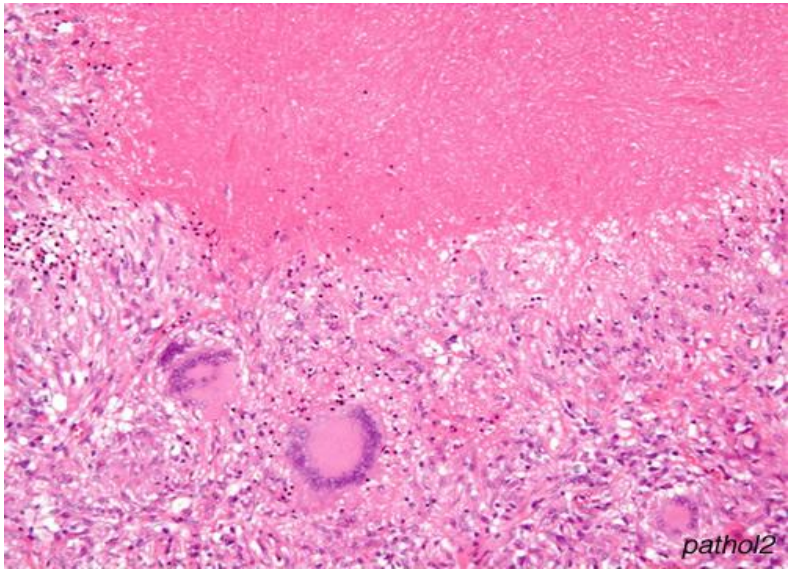
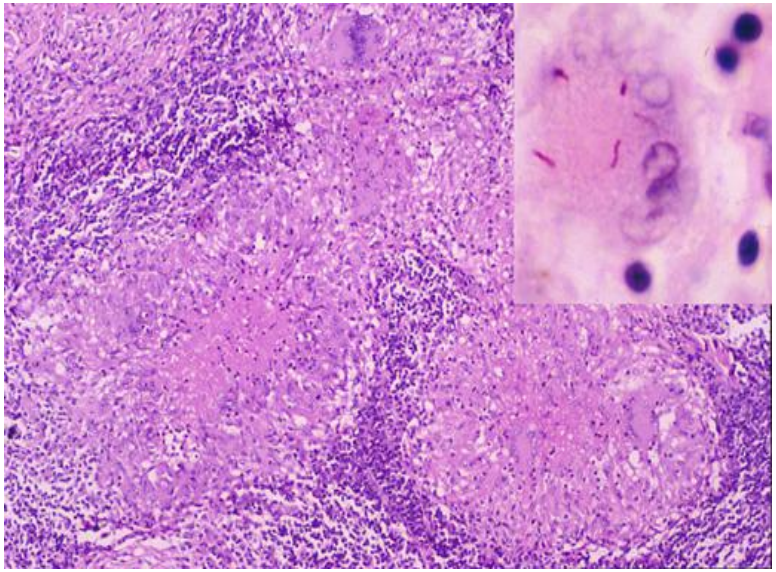








Neoplastic proliferations of white cells

Lymphoid neoplasms : (stages in lymphocyte differentiation)

Myeloid neoplasms : (hematopoietic stem cell of myeloid lineage)

Histiocytic : (macrophages & dendritic / reticulum cells)

Lymphoid Neoplasms

Leukemia – widespread involvement of bone-marrow

Lymphoma – proliferations arising as discrete tissue masses

HOWEVER THE LINE BETWEEN LYMPHOCYTIC LEUKEMIA AND LYMPHOMA OFTEN BLURS

Malignant lymphomas

- Malignant neoplasms of lymphoid origin
- Divided into Hodgkin's and Non-Hodgkin's types
- All HL and 2/3rd of NHL occur in lymph nodes
- Lymphoid neoplasms show some degree of T or B cell differentiation
- Associated with immune system abnormalities
- Neoplastic cells can recapitulate behavior of normal counterparts

CLINICAL FEATURES

- **Lymphadenopathy**：Enlarging mass(es), typically painless, at sites of nodal tissue
- **Compression, infiltration** of hollow organs
  - Pain, obstruction, perforation
- **Interference with normal organ function-**
  - Solid organ infiltration- kidneys, liver, bone marrow
- **Systemic symptoms**
  - Fever > 38^C
  - Night sweats
  - Weight loss >10% body weight

‘B symptoms”

- If marrow infiltrated, can have **leukemic** component

Aetiologic & pathogenetic factors

1.Non-random chromosomal translocations & oncogenes (Ag.receptor gene expression)

2.Inherited genetic factors-HLA types & in identical twin in HD

3.**Viruses** :

i) HTLV-1 : Adult Tcell leukemia /lymphoma

ii) EBV : Burkitt'slymphoma, 30-40% of HD, many B cell lymphomas

iii) KSHV : B cell lymphomas of pleural cavity with effusion

4.Environmental agents *(i and ii –chronic inflammation)*

i) H.Pylori infection – gastric B cell lymphoma

ii) Gluten sensitive enteropathy – intestinal T cell lymphoma

iii) HIV infection(B cell stimulation) - B cell lymphoma

5.Iatrogenic factors *:*

Radiotherapy & certain forms of chemotherapy

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*

- **Final result**

  - *Difficult area to teach*
  - *Difficult to remember*
  - *Job security for me*

Classifications

I. *Rappaport classification*

- Nodular lymphoma
- Diffuse lymphoma

II. *Lukes – Collin's classification*

- B cell lymphoma
- T cell lymphoma

III. *Working formulation for clinical usage*

1. Low grade NHL : 5 yr survival 50 – 70%
2. Intermediate grade NHL : 5 yr survival 35 – 45%
3. High grade NHL : 5 yr survival 25 – 35%

IV. *REAL Classification*

1. Leukemias & lymphomas of B cell origin
2. Leukemias & lymphomas of T cell origin

WHO Classification

A. **Precursor B cell neoplasms (immature B cells)**

Precursor B lymphoblastic leukemia/lymphoma

B. **Peripheral B cell neoplasms (mature B cells)**

Chronic lymphocytic leukemia/SLL

Follicular lymphoma

Diffuse large B cell lymphoma

Burkitt's lymphoma

C. **Precursor T cell neoplasms (immature T cells)**

Precursor T lymphoblastic leukemia/lymphoma

D. **Peripheral T cell & NK cell neoplasms (mature T cells)**

Peripheral T cell lymphoma

Mycosis fungoides / Sezary syndrome

Anaplastic large cell lymphoma

NK T cell lymphoma

E. **Hodgkin's lymphoma**

Precursor B cell neoplasms (immature B cells)

Acute lymphoblastic leukemia/lymphoma

B cell → children mostly affected, leukemia

T cell → adolescent, adults infected with HIV, lymphoma

Normal tissue architecture effaced by LYMPHOBLASTS

Prognosis:

90% B cell ALL – complete remission

T cell ALL in adults – fatal within months – 1 yr

Peripheral B cell neoplasms (mature B cells)

1. Chronic lymphocytic leukemia/SLL

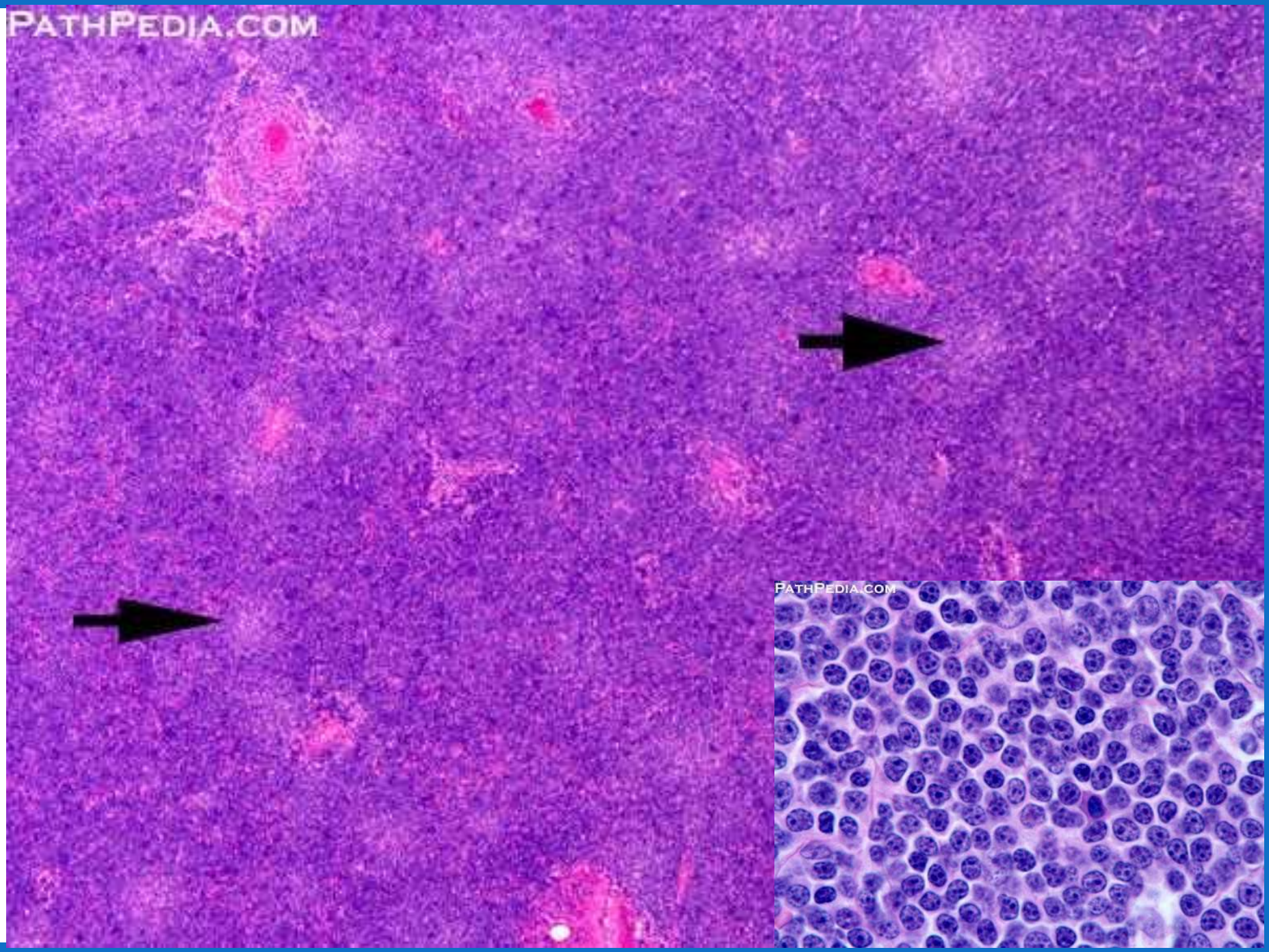
CLL – most common leukemia of adults

SLL – 4% of NHL

LN architecture diffusely effaced by SMALL LYMPHOCYTES

CLL-no of lymphocytes & smudge cells

Median survival – 4 to 6 yrs, variable prognosis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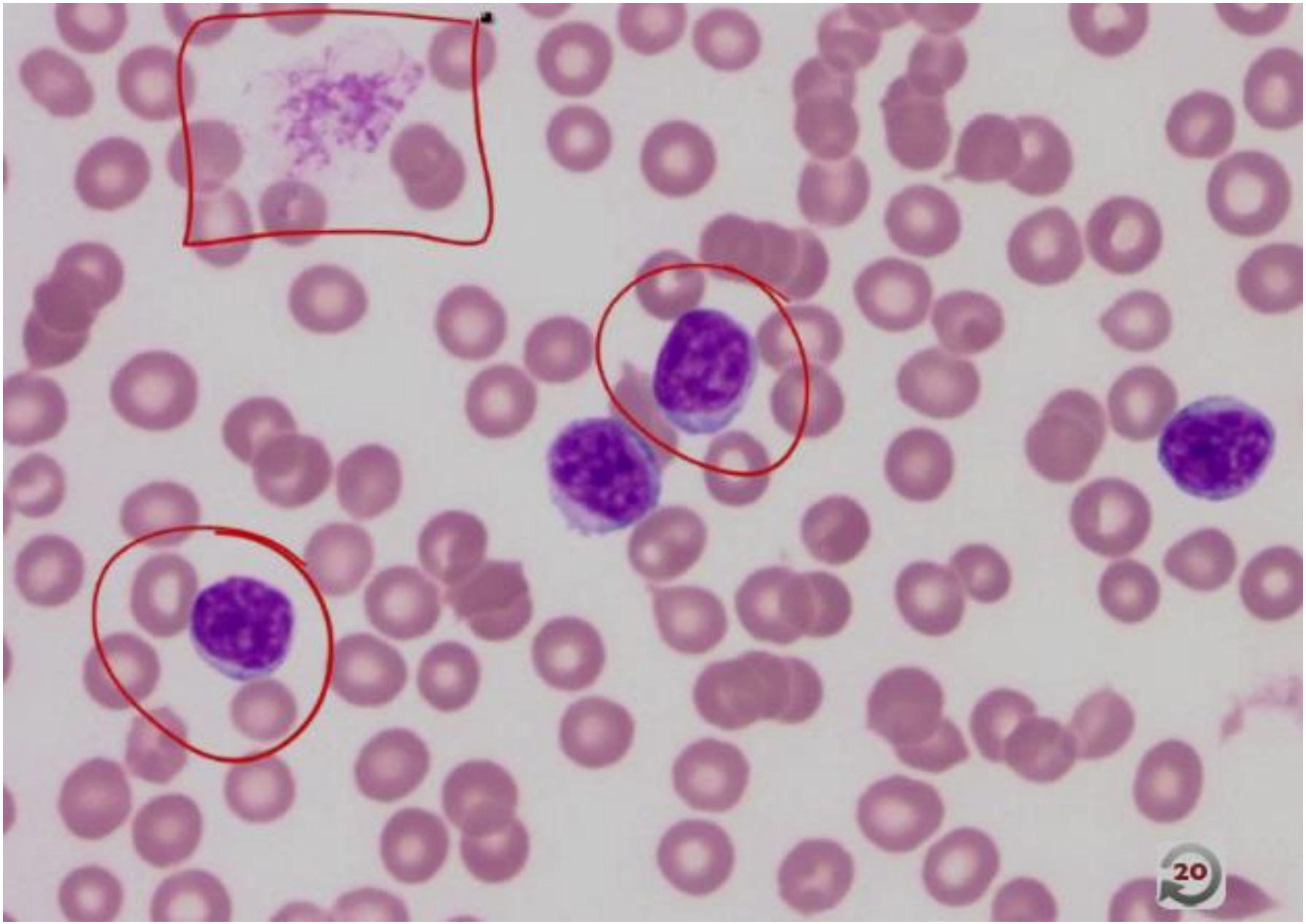
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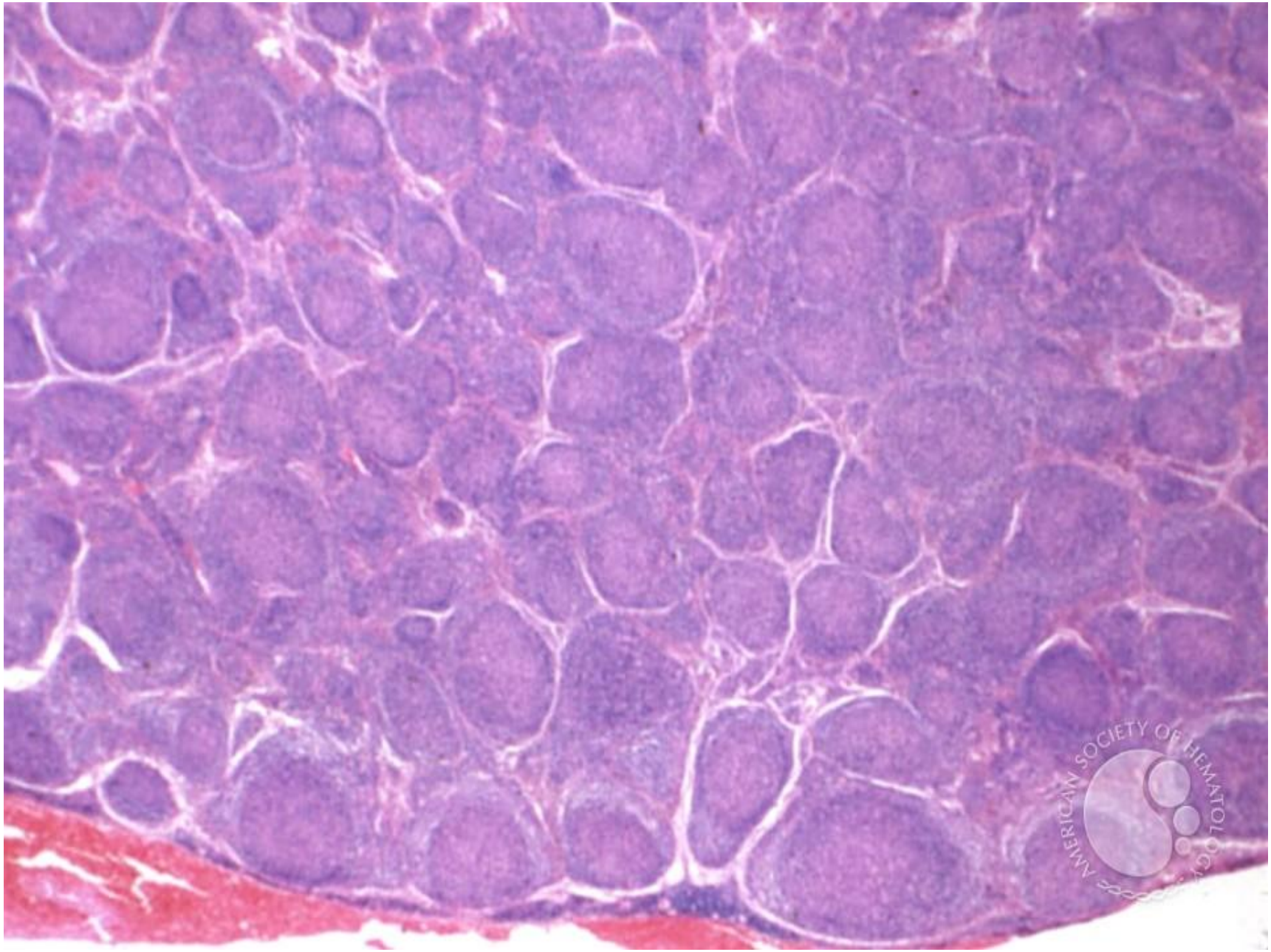
Peripheral B cell neoplasms (mature B cells)

2. Follicular lymphoma

- Common, 45% of NHL, Middle age, both sexes,
- Painless generalized LNpathy
- Neoplastic cells closely resmble normal germinal centre B cells, nodular pattern seen, incurable.
- Follows indolent waxing & waning course
- Median survival 7-9 yrs,
- Palliative treatment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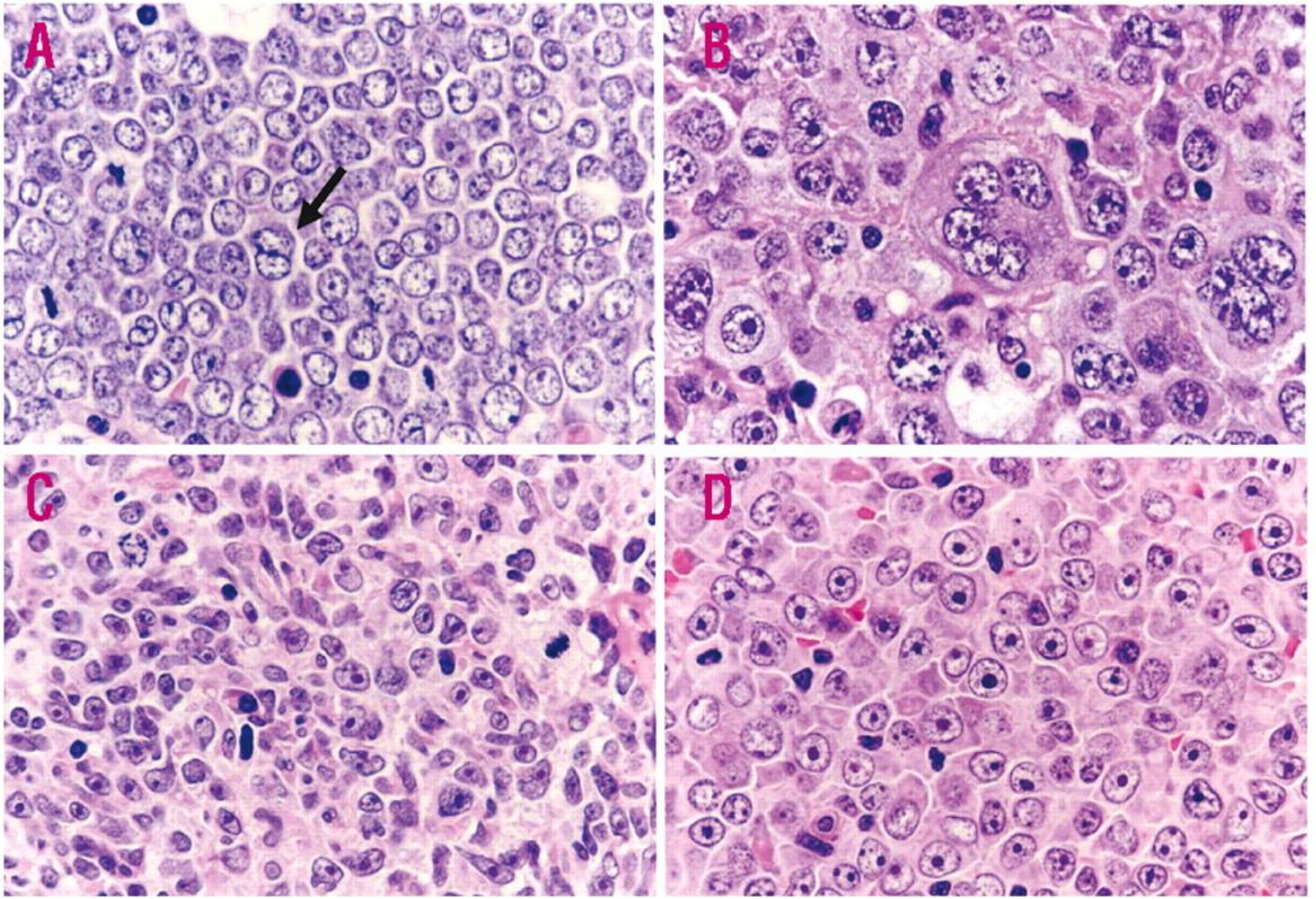
Peripheral B cell neoplasms (mature B cells)

3.Diffuse large B cell lymphoma

- 20% of NHL, 6th decade, male preponderance
- Large cell size (4-5times of SL) & diffuse pattern rapidly enlarging, symptomatic mass
- Fatal if untreated.
- With aggressive chemotherapy complete remission in 60-80% of cases
- Genetics- Dysregulation of bcl-6, t(14:18) translocation


A
B
C
D

Peripheral B cell neoplasms (mature B cells)

4.BURKITT'S LYMPHOMA

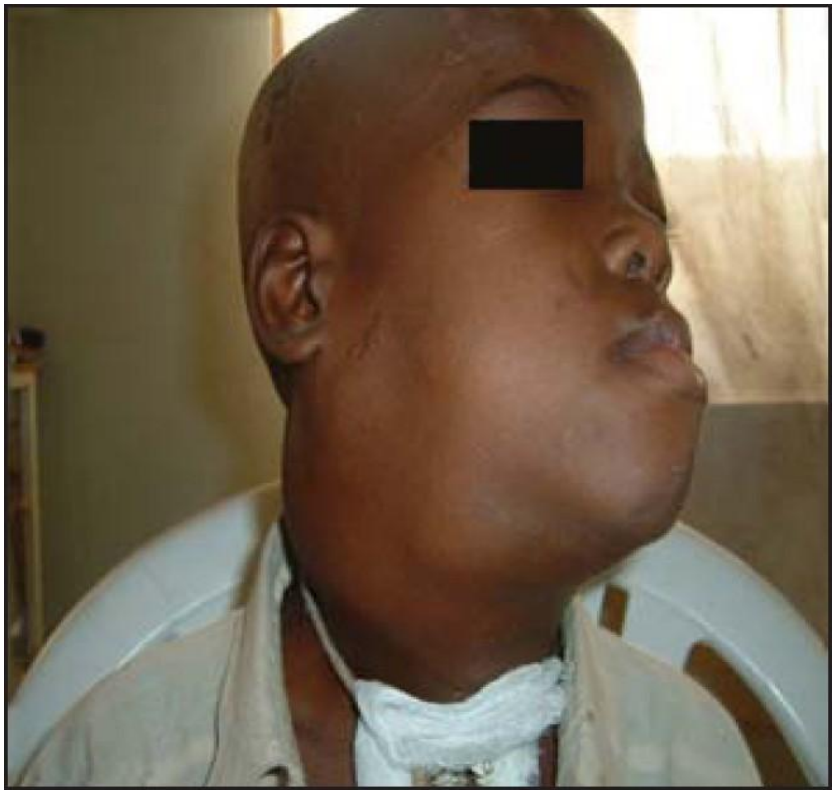
- Non Hodgkin's B cell lymphoma of small noncleaved cell type, associated with EBV infection
- Ist lymphoma in which cytogenetic abnormality was detected
- **Variants**
- Endemic (African) – all cases associated with EBV
- Sporadic (non endemic) – 15-20% cases associated with EBV
- In individuals infected with HIV – 25% cases associated with EBV

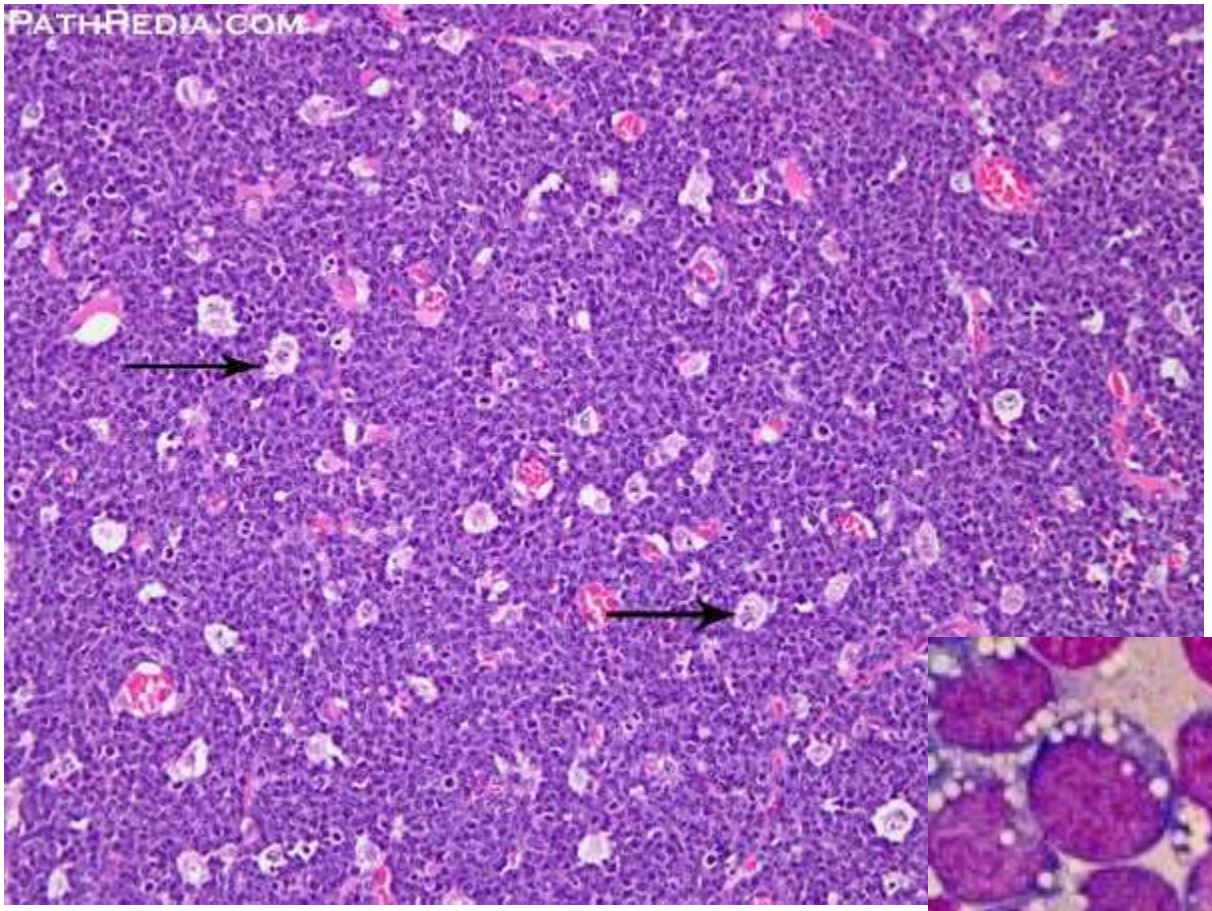
Pathogenesis

- Immortalisation of EBV in B lymphocytes of infected patients
- Continuous stimulation of lymphocytes by EBV bearing B cells
- Reciprocal chromosomal translocation 8:14
- Rapid tumor growth with increased growth fraction and short doubling time

C/F

- Mean age – 7 years
- M:F=2:1
- Jaw/ orbital bone -60% cases
- LN- abdominal followed by cervical
- AIDS associated – CNS involvement

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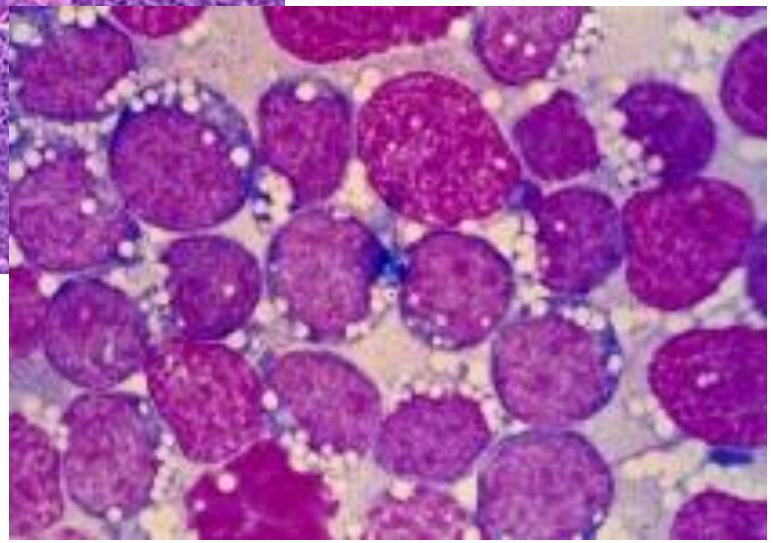


Precursor T cell neoplasms (immature T cells)

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

MICRO -

- Benign equivalent immature T cells of thymus
- Histology: Diffuse infiltration of thymus/adjacent lymph nodes

Peripheral T cell & NK cell neoplasms (mature T cells)

Peripheral T cell & NK cell neoplasms

15 % of NHL in USA & Europe
More common in Asia

Mycosis Fungoides/ Sezary syndrome

Marked predilection for skin

Inflammatory or premycotic phase, Plaque phase and Tumor phase
Infiltration of the epidermis, upper dermis by neoplastic cells having cerebriform appearance (nuclear membrane infolding)

Sezary syndrome

Involvement of skin(exfoliative erythroderma) & leukemia of sezary cells (also with cerebriform nucleii)
Indolent tumours with median survival of 8-9 yrs

Immunohistochemistry (IHC markers)

Immune cell Ags (markers),using monoclonal antibodies:

Primarily T cell associated :

CD1, CD3, CD4, CD5, CD8

Primarily B cell associated :

CD10, CD19, CD20, CD21, CD23 CD 79a

Staging of NHL

Ann-Arbor staging more useful for Hodgkin's lymphoma

Spread is less predictable in NHL as systemic disease has occurred at time of diagnosis

Provides useful prognostic information but not important in guiding treatment

HODGKIN'S LYMPHOMA

DEFINITION

- A lymphoma characterized by a heterogenous cellularity comprising a minority of specific neoplastic cells and a majority of reactive non-neoplastic cells

C/F

- Age-bimodal distribution;b/w 15-34 yrs & 54 yrs
- M>F
- Less common than NHLs in HIV pts
- Etiology-EBV infection is implicated as R-S cells are EBV+ in 40% to 50% cases

- Cervical and supraclavicular nodes are commonly involved
- Usually contiguous spread
- Non contiguous spread in case of vessel invasion
- Enlarged LN- non painful, non tender
- Immune deficiency symptoms
- B symptoms

HP/F

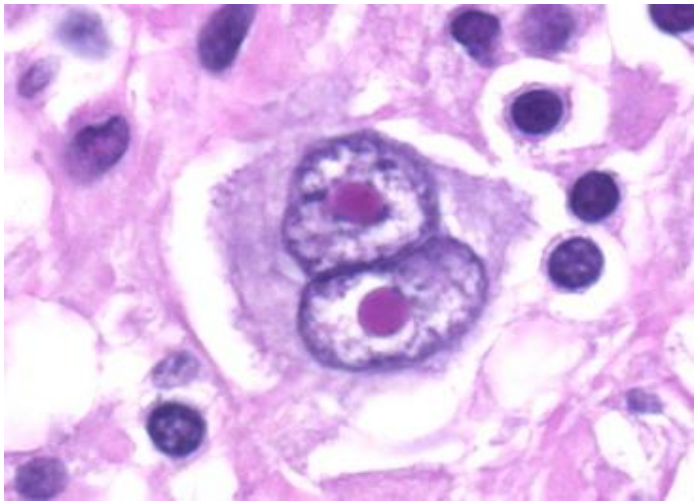
Cell types

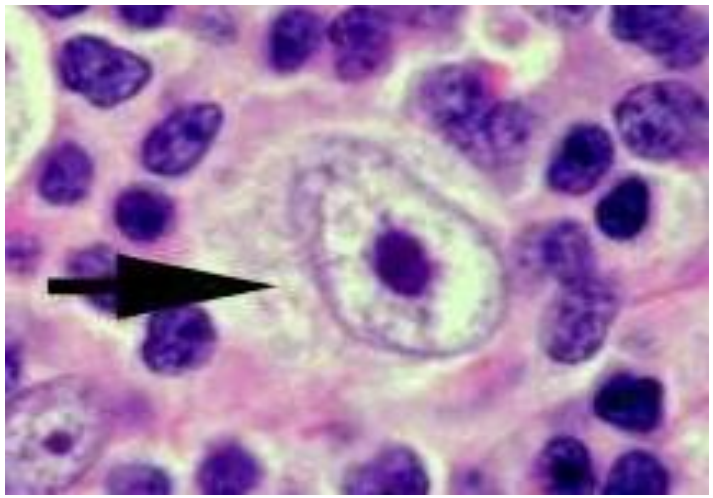
1) Non neoplastic cells

- Represent immune reaction to neoplastic cellular component
- Lymphocytes with small round nucleus and rare mitoses is predominant
- Majority are CD_4+ T cells
- Occasional histiocytes, fibroblasts, immunoblasts, plasma cells, neutrophils and eosinophils are seen
- Eosinophils-constant and characteristic component of NS & MC types- 'eosinophilic microabscesses'
- Epitheloid granulomas in 10% cases
- Increased no of epitheloid cells in MC type

2. Neoplastic cells

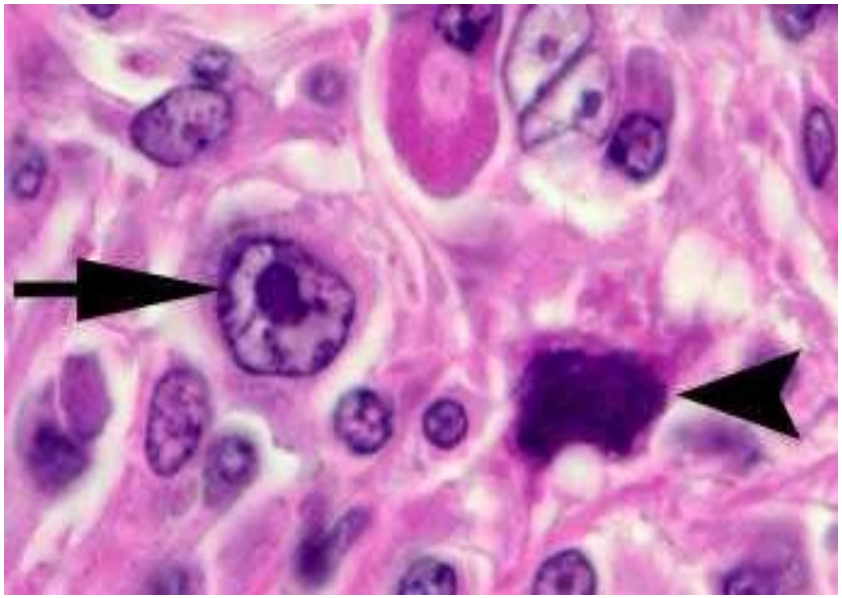
- Reed Sternberg cells are pathognomic, typical cells are 20-60 Microns in diameter
- Variable amount of amphophilic cytoplasm
- Large nuclei with thick nuclear membrane. 2 nuclei- mirror image
- Single **prominent eosinophilic nucleolus** – owl eye appearance
- May show multipolar mitoses
- Mononucleated cells with prominent eosinophilc nucleolus-'Hodgkin cell"
- Constitute 1-3% of tumor volume

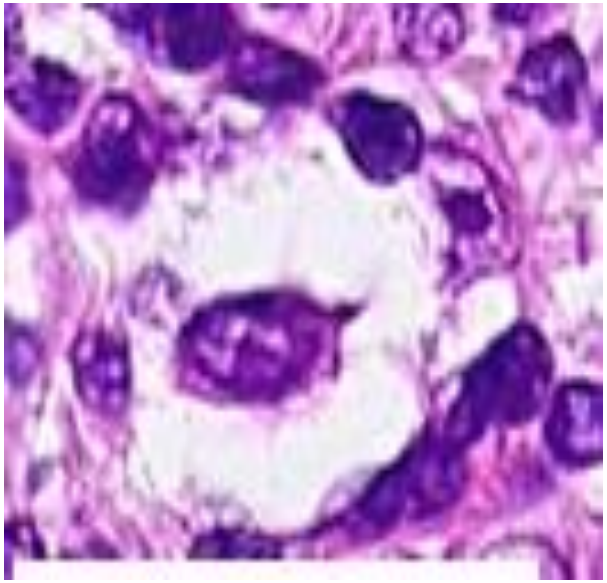


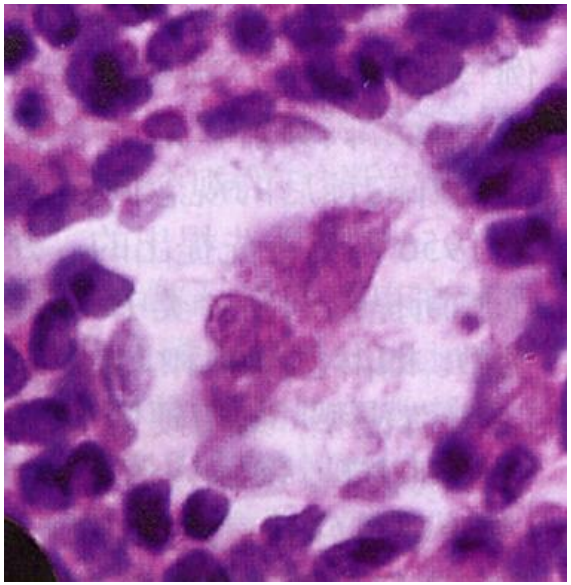


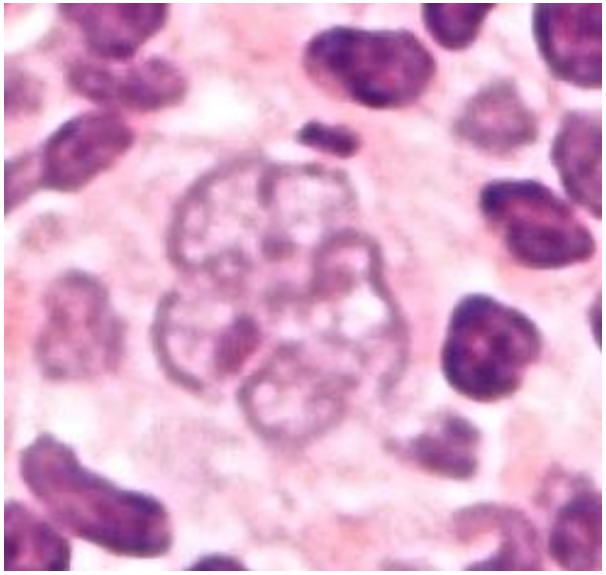
RS cell variants

- Hodgkin cell- mononuclear
- Lacunar variant
- Mummified variant
- Anaplastic variant
- L H cells-pop corn cells







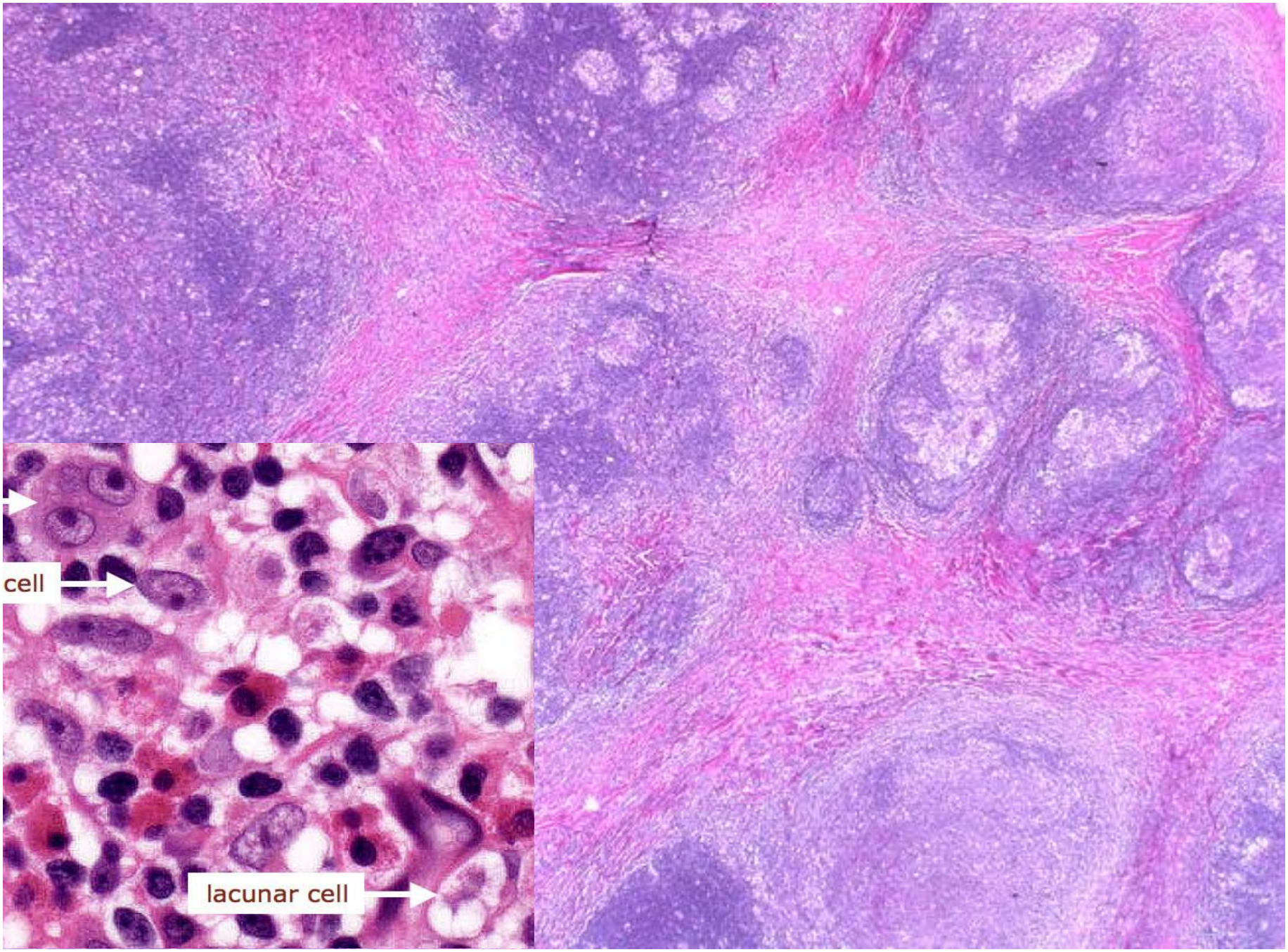


NODULAR SCLEROSIS TYPE

- Most common especially in **Young women**

Diagnostic criteria

- *Lacunar cells*- single/sheets
- Sclerosis- defining feature- broad interconnecting *bands of collagen*-originate from capsule and divide LN into nodules of varying sizes and shapes
- *RS cells* in variable numbers
- Phases- cellular phase to fibrotic phase
- Syncytial Variant of NS -Extreme form of cellular phase-Numerous RS cells and Hodgkin's cells arranged in clusters and sheets, Central necrosis-Resembles melanoma/metastatic carcinoma


cell
lacunar cell

LYMPHOCYTE RICH

- Few RS cells and HC within a mass of lymphocytes and only few eosinophils and neutrophils
- Incidence-6%

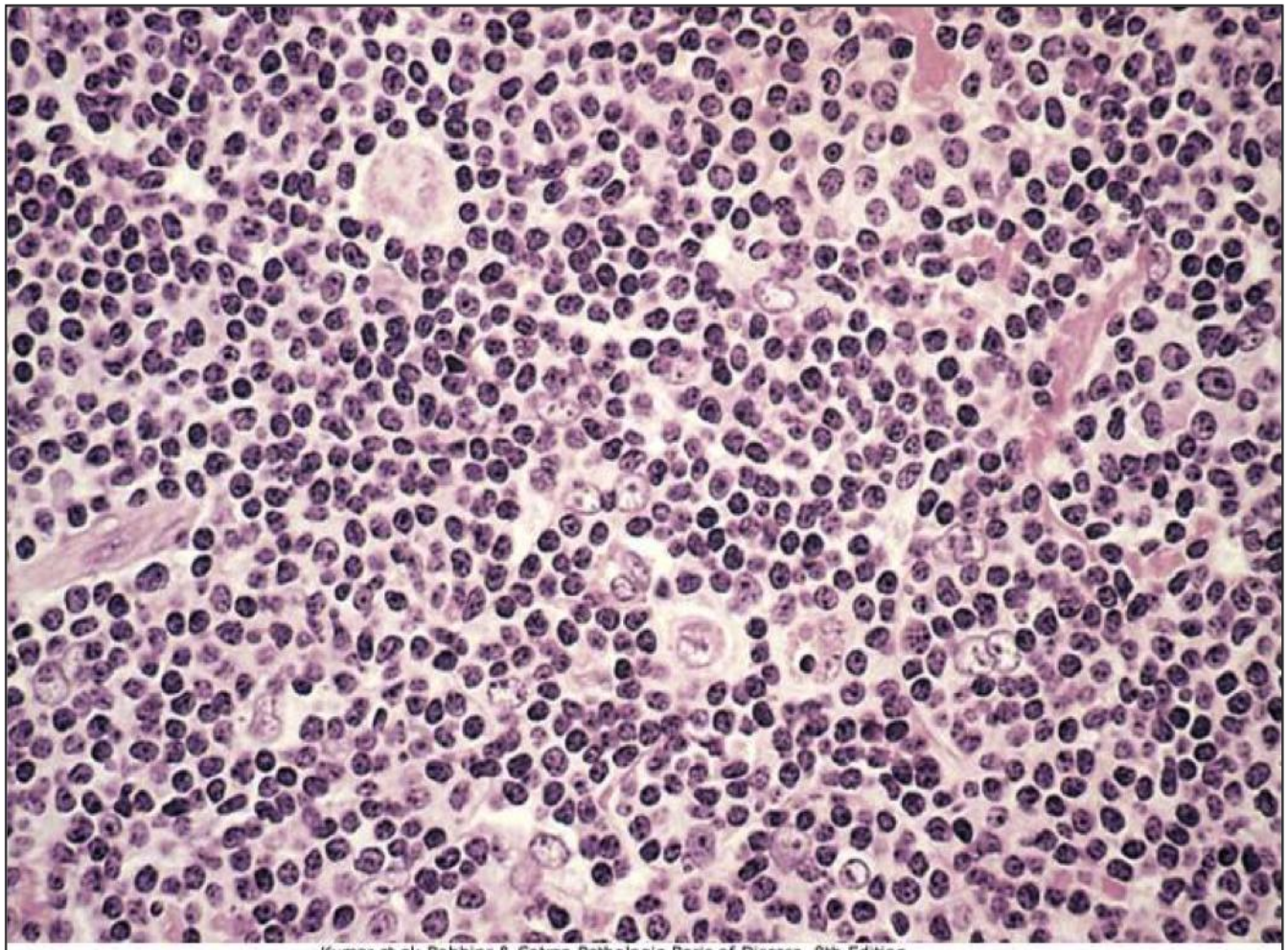
Diagnostic-

1.< 5 RScells/hpf

2. Bad prognosis-

Survival 2-3 yrs

Post diagnosis

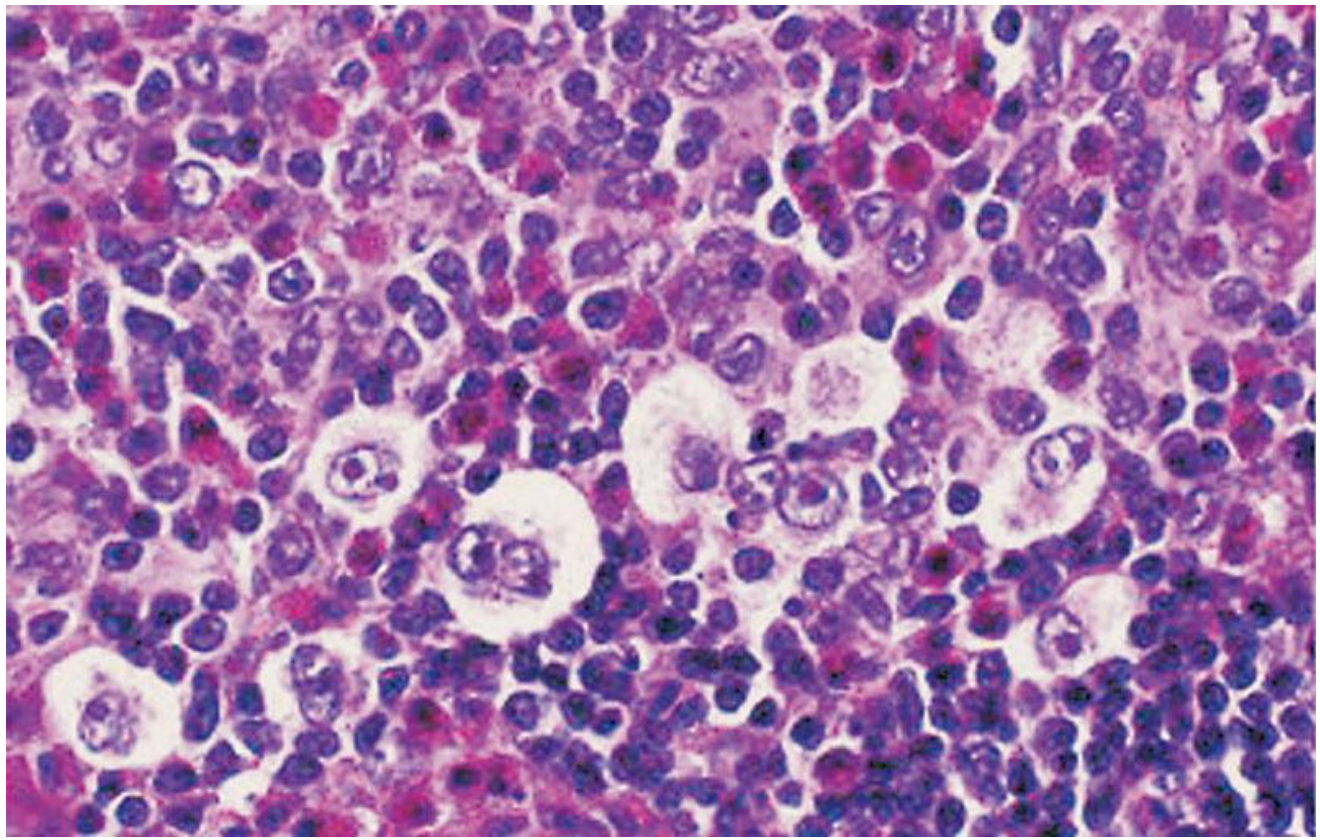


MIXED CELLULARITY

- Heterogenous cell population- lymphocytes, plasma cells, histiocytes, eosinophils, HC, Rs cells with Moderate to diffuse fibrosis
- Common in young /elderly /AIDS pts
- Involves whole / large areas of LN
- Total loss of architecture
- Foci of necrosis

Diagnostic criteria

- 5-15 RS & HC/hpf



LYMPHOCYTE DEPLETION

- Most aggressive form of HL, worst prognosis
- Older pts
- Short median survival(4-5 months posr diagnosis)
- Subtypes-
- 1. Diffuse Fibrosis
- 2. Reticular

Diagnostic criteria

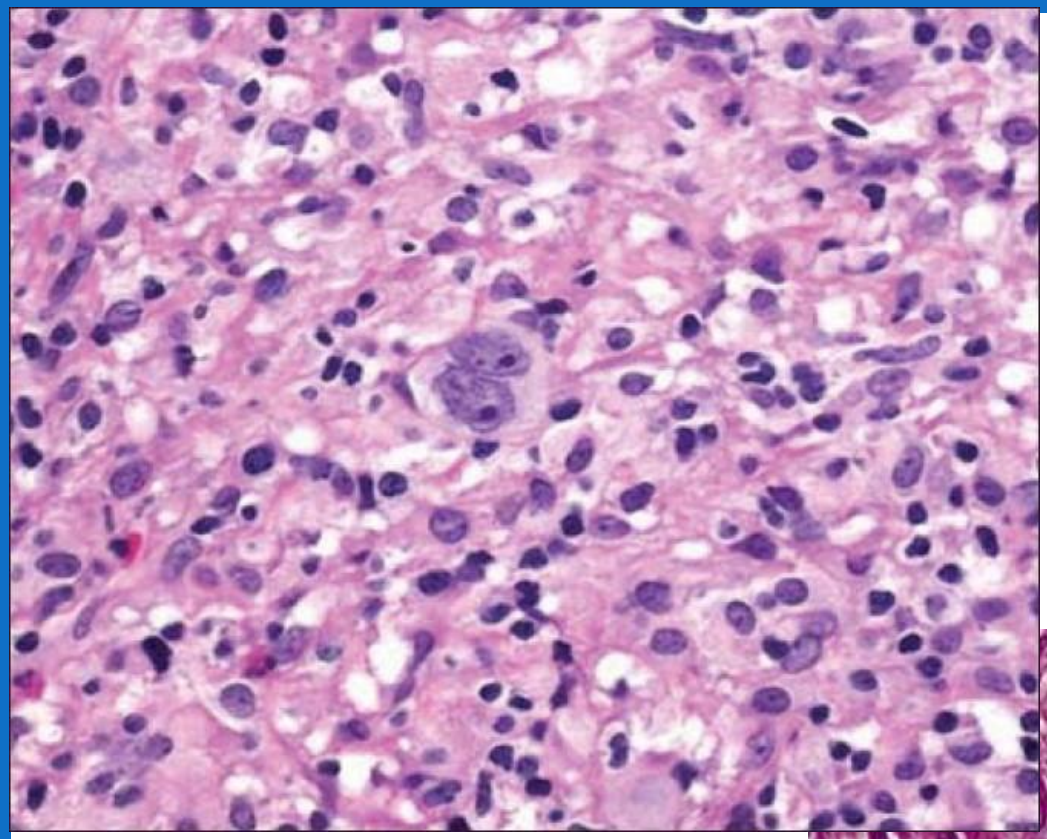
- RS & HC > 15 cells/hpf

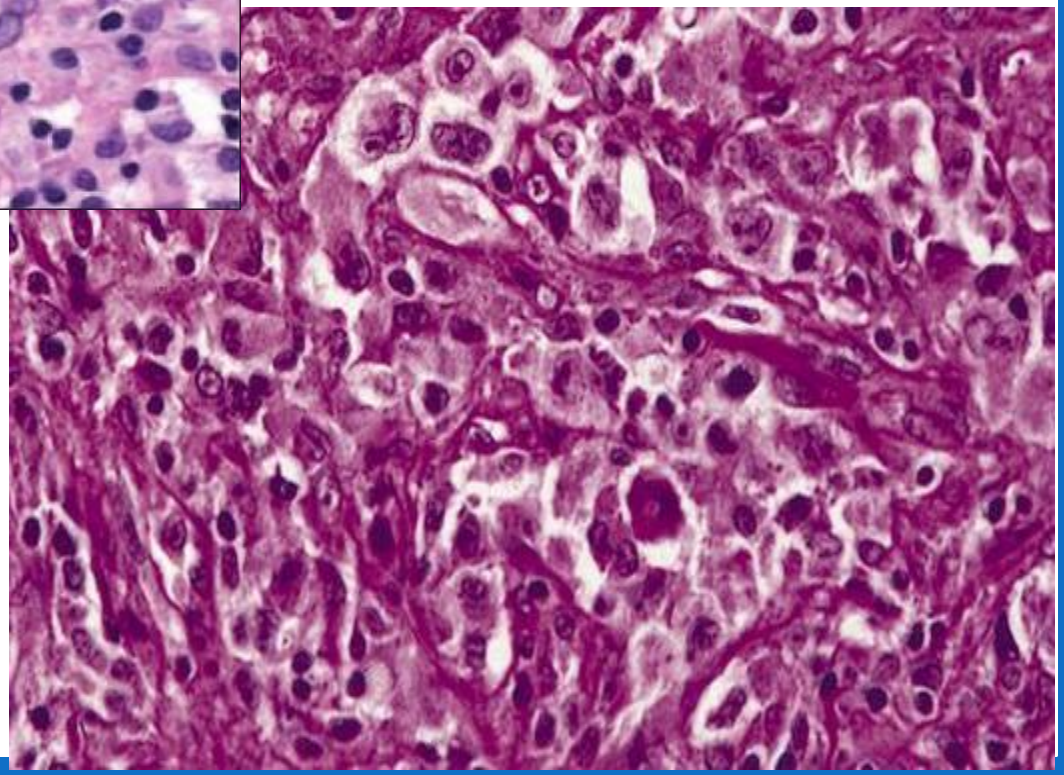
Diffuse Fibrosis

- Develops spontaneously or as a result of radiation or chemotherapy
- Poorly cellular structureless LN architecture
- Normal parenchyma replaced by fibrous tissue, scattered RS cells/residual lymphocytes
- Spindle cells
- Bizzare RS cells

Reticular subtype

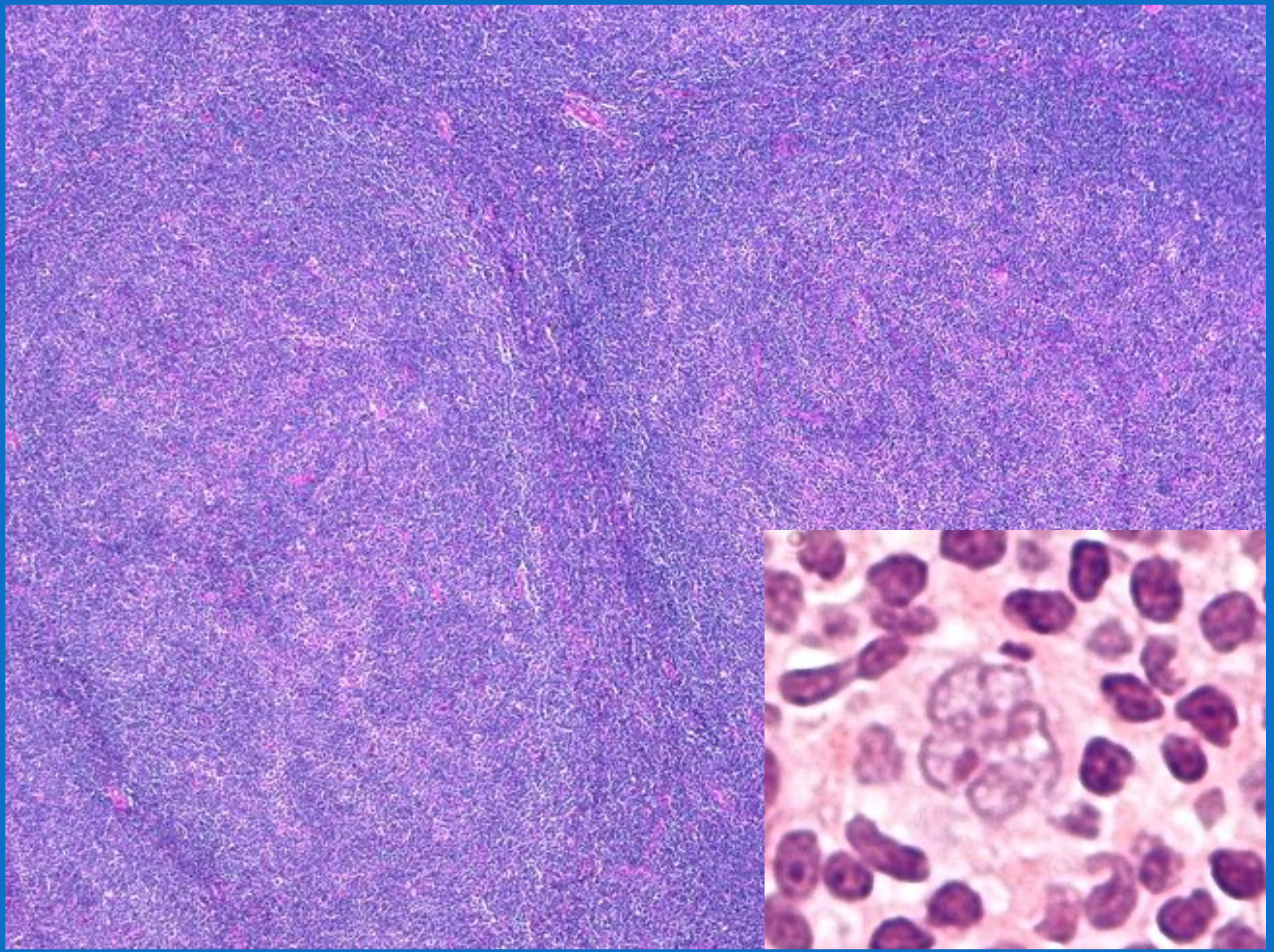
- Hypercellular
- Normal LN architecture obliterated by pleomorphic RS cells/variants
- Eosinophils, neutrophils, macrophages
- Foci of necrosis, minimal fibrosis
- Characteristic capsule / perinodal invasion





NODULAR LYMPHOCYTE PREDOMINANT

- Also c/d paragranuloma
- Nodular lymphoproliferation with clinicopathological features of both HL and low grade B cell lymphoma
- 2-6% of HL
- Aggressive Transformation to DLBCL has been reported
- Good prognosis
- 2 patterns – nodular and diffuse



IHC

- RS cells & variants-

  CD15+, CD30+

  CD45-,CD20-,EMA-, B cell markers-

- Nodular lymphocyte predominance type-

  LH cells (Popcorn RS cells) - CD45+, CD 20+, B cell markers+

Hodgkin's Lymphoma	Non Hodgkin's Lymphoma
Single axial gp of LNs	Multiple peripheral LNs
Orderly spread by contiguity	Non contiguous spread
Mesentric nodes & Waldeyer's ring rarely involved	Commonly involved
Extranodal involvement uncommon	common
BM involvement uncommon	common
B cell origin	90% B cell, 10% T cell
R-S cells seen	R-S cells not seen
Constitutional (B) symptoms common	uncommon
Spill over -- never	Can occur
Prognosis – better (70-85% cure)	Prognosis – bad (30-40 % cure)

Hodgkin's Lymphoma	Non Hodgkin's Lymphoma
Associated with EBV	May be associated with HIV and autoimmune diseases
Bimodal distribution. Young adult of 15-30 and > 55 years	Can occur in children and adults
> 80% are diagnosed in stag I & II	> 85% in stage III or IV
Nodal Groups involved Thoracic 65-85% Para-aortic 25-35% Mesenteric 5%	 Thoracic 25-40% Para-aortic 45-55% Mesenteric 50-65%

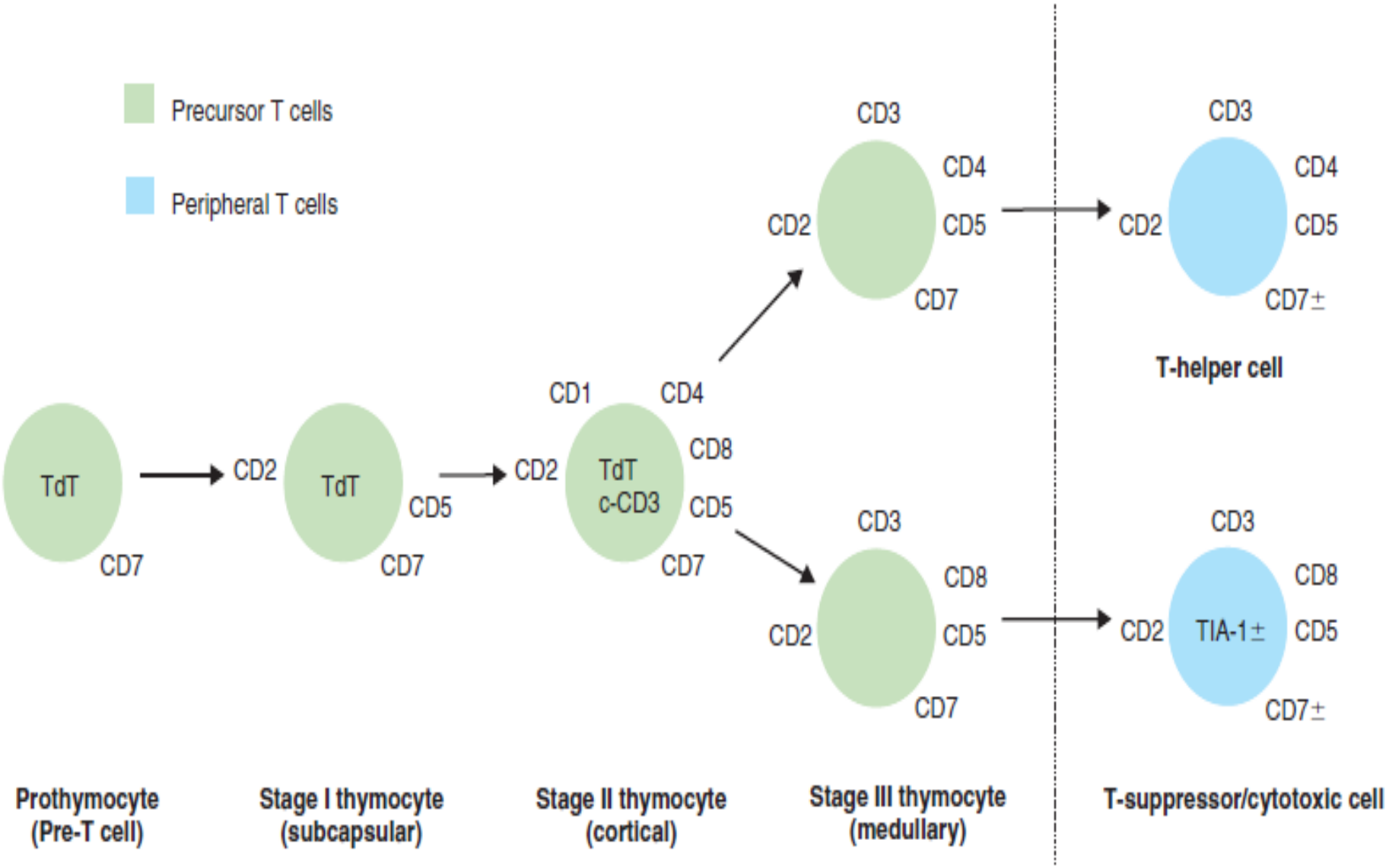


FIGURE 21A-4 ■ Development of T lymphocytes and the changes in immunophenotypic profile at the different stages of differentiation. Markers shown within the circles (cells) are expressed in the cytoplasm (*c-*) or nucleus, whereas markers shown outside the circles are expressed on the cell surface. *TdT,* Terminal deoxynucleotidyl transferase.

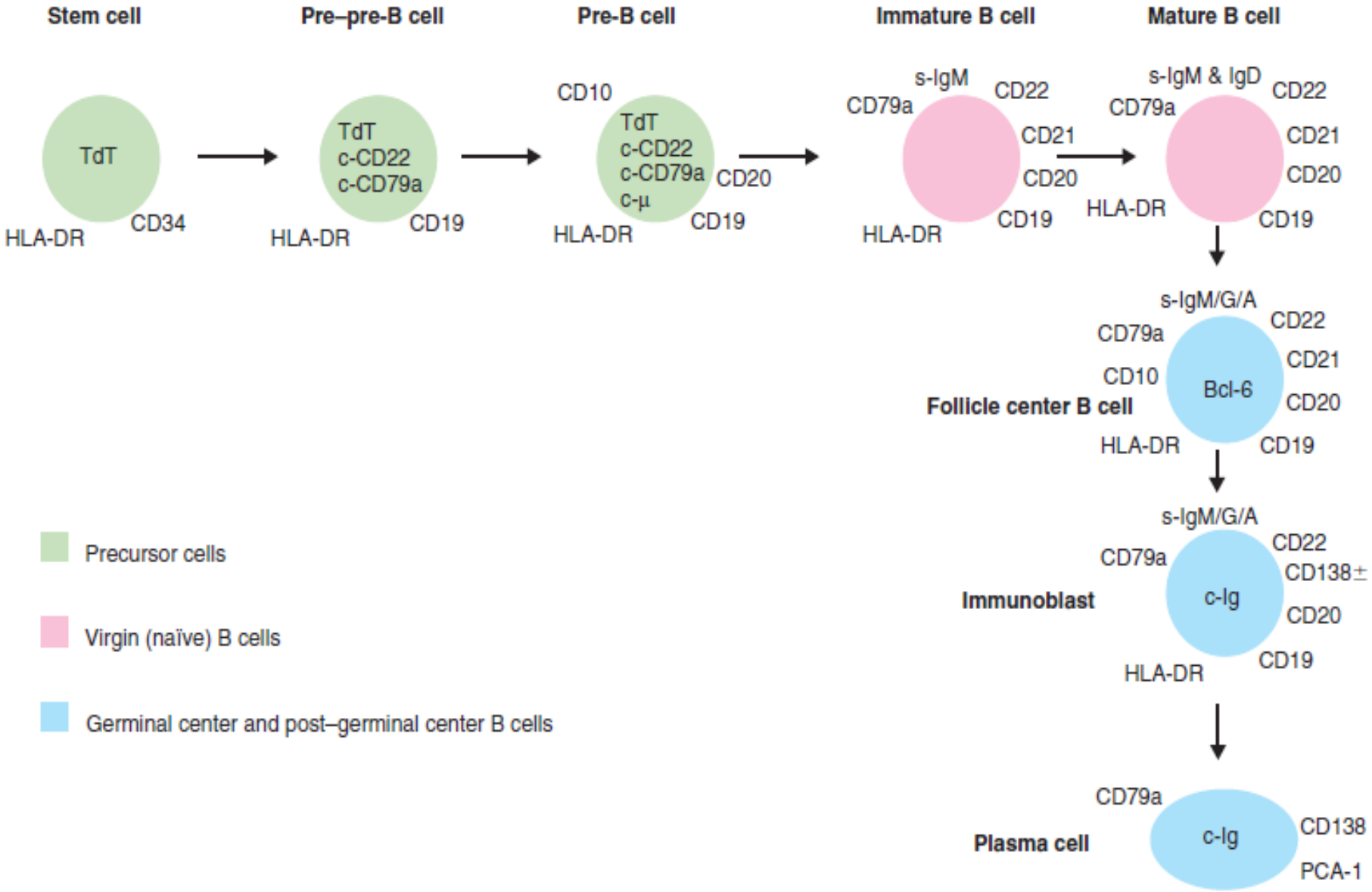


FIGURE 21A-3 ■ Development of B lymphocytes and the changes in immunophenotypic profile at the different stages of differentiation. Markers shown within the circles (cells) are expressed in the cytoplasm (*c-*) or nucleus, whereas markers shown outside the circles are expressed on the cell surface (*s-*). Note that the common surface B-cell markers are lost with maturation into plasma cells. *Ig,* Immunoglobulin; *TdT,* terminal deoxynucleotidyl transferase.

Hodgkin's Lymphoma

- involves single node & spreads to contiguous nodes
- presence of neoplastic Reed-Sternberg(R-S) giant cells
- neoplastic R-S giant cells derived from germinal centre B cells
- common in young adults

Classification

1. **Classical subtypes** – (R-S cells CD15 & CD30 + ve and CD45 –ve)
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte rich
   - Lymphocyte depletion
2. **Nodular lymphocytic predominance (NLPHL)**

(R-S cells CD20 & CD45 + ve and CD15 & CD30 –ve)

Identification of R-S cells is essential for the histologic diagnosis though similar cells can occur in Inf.mononucleosis ,NHLs,solid tissue cancers.

Thus although R-S cells are requisite for the diagnosis, they must be present in an appropriate background of non neoplastic inflammatory cells viz.small (T) lymphocytes,plasma cells,eosinophils and macrophages which are benign.

R-S cells

1.Classical – 15-45 micrometer in size
multiple /bilobed nucleus with eosinophilic nucleolus
with clear halo around it – OWL EYE appearance
abundant amphophilic cytoplasm
Mixed cellularity type

2.Lacunar – nucleus lying in empty hole due to shrinkage of cytoplasm
artifact ,in formalin fixed tissues (not in Zenker's fluid fixative)
Nodular sclerosis type

3. Pleomorphic – pleomorphic cells with atypical nuclei
Lymphocyte depletion type

4.Lymphohistiocytic / popcorn / polypoid – NLPHL type
– cells with polypoid nuclei & abundant cytoplasm

5.Mononuclear / atypical Hodgkin's cells
– Lymphocyte rich type
– single,round or oblong nucleus with large inclusion like nucleus

Inverse proportion between no. of lymphocytes & no of R-S cells