LYMPHOID TISSUE DISORDERS

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Lymphoid Tissue

Lymphoid tissues (L.T), which is either Primary or Secondary tissue organs.

1- **Primary** lymphoid organs;

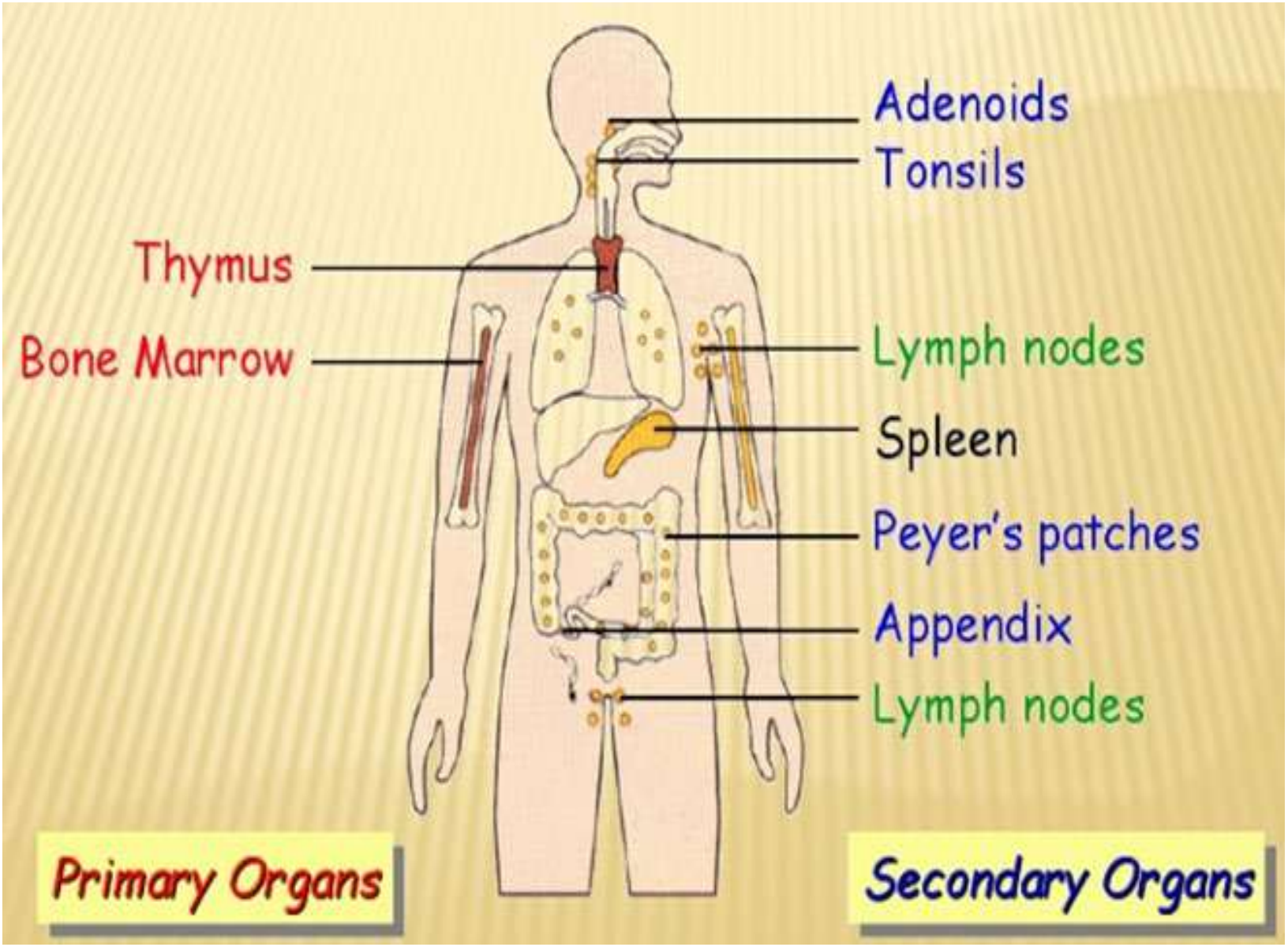
a- Bone marrow; where both T and B lymphocytes are derived from hematopoietic stem cells and where B lymphocytes also mature.

b- Thymus; which is the site of T-cell maturation.

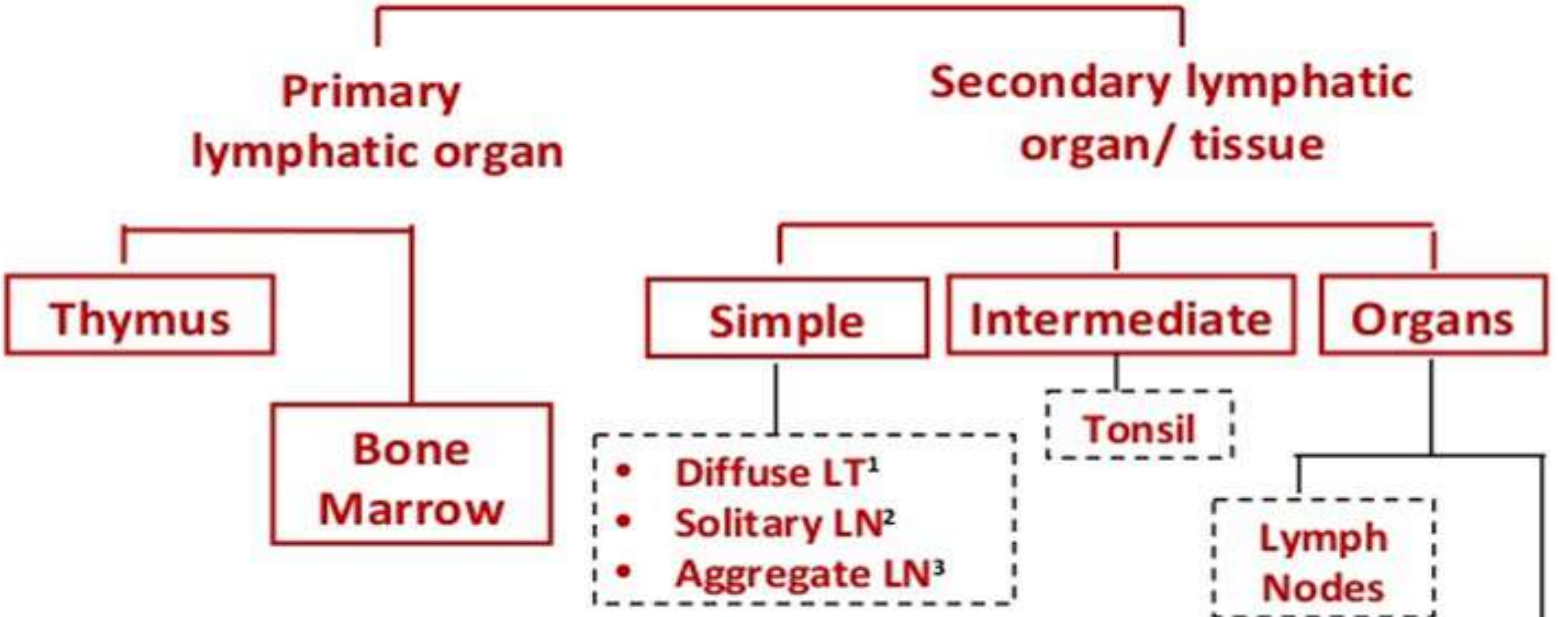
2- **Secondary** lymphoid organs; Spleen, lymph nodes and mucosa- associated lymphoid tissue (MALT).

- Trap and concentrate foreign substances.

- The major sites of interaction between lymphocytes and microorganisms.


Adenoids
Tonsils
Thymus
Bone Marrow
Lymph nodes
Spleen
Peyer's patches
Appendix
Lymph nodes
Primary Organs
Secondary Organs

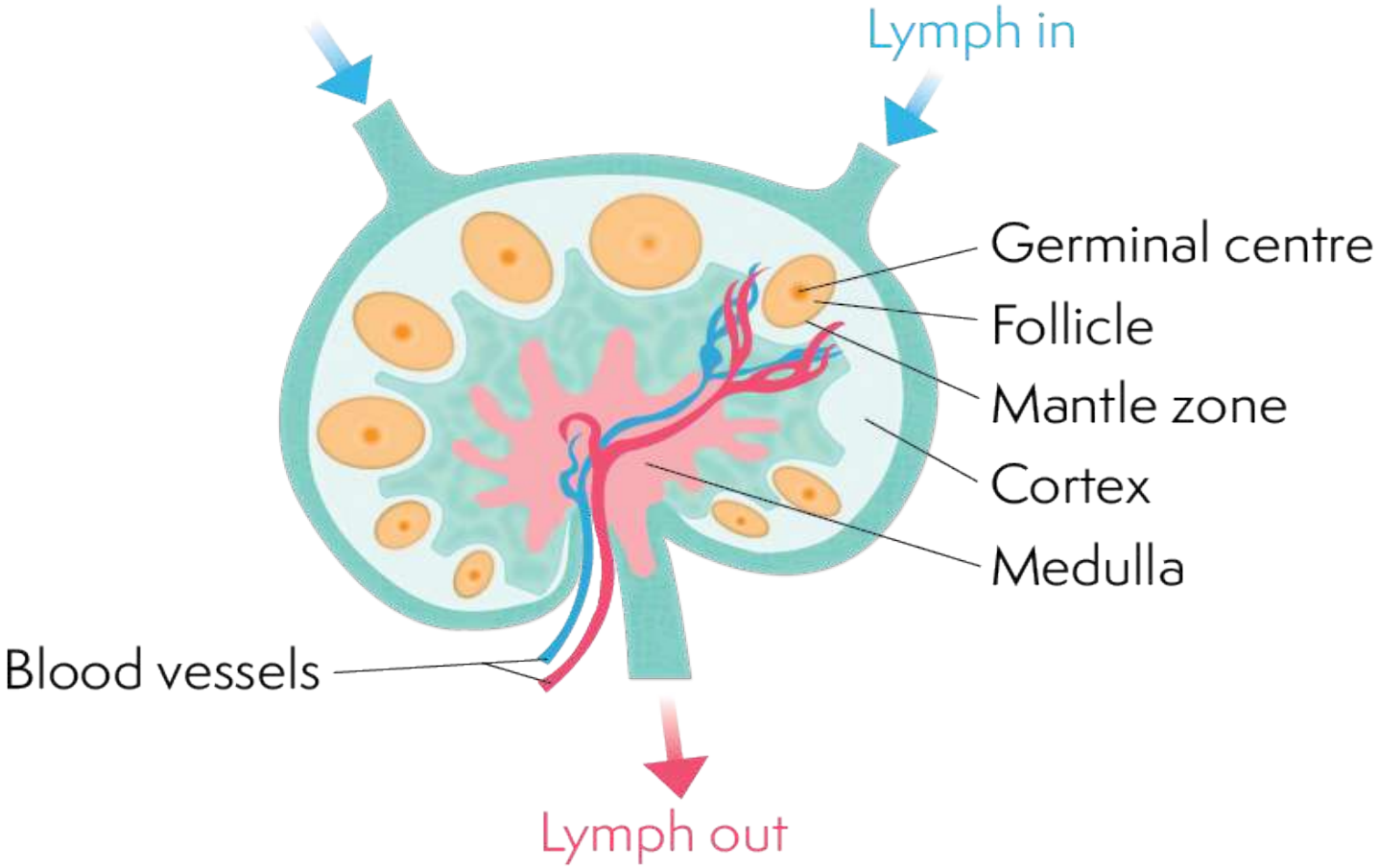
Lymphoid tissue classification

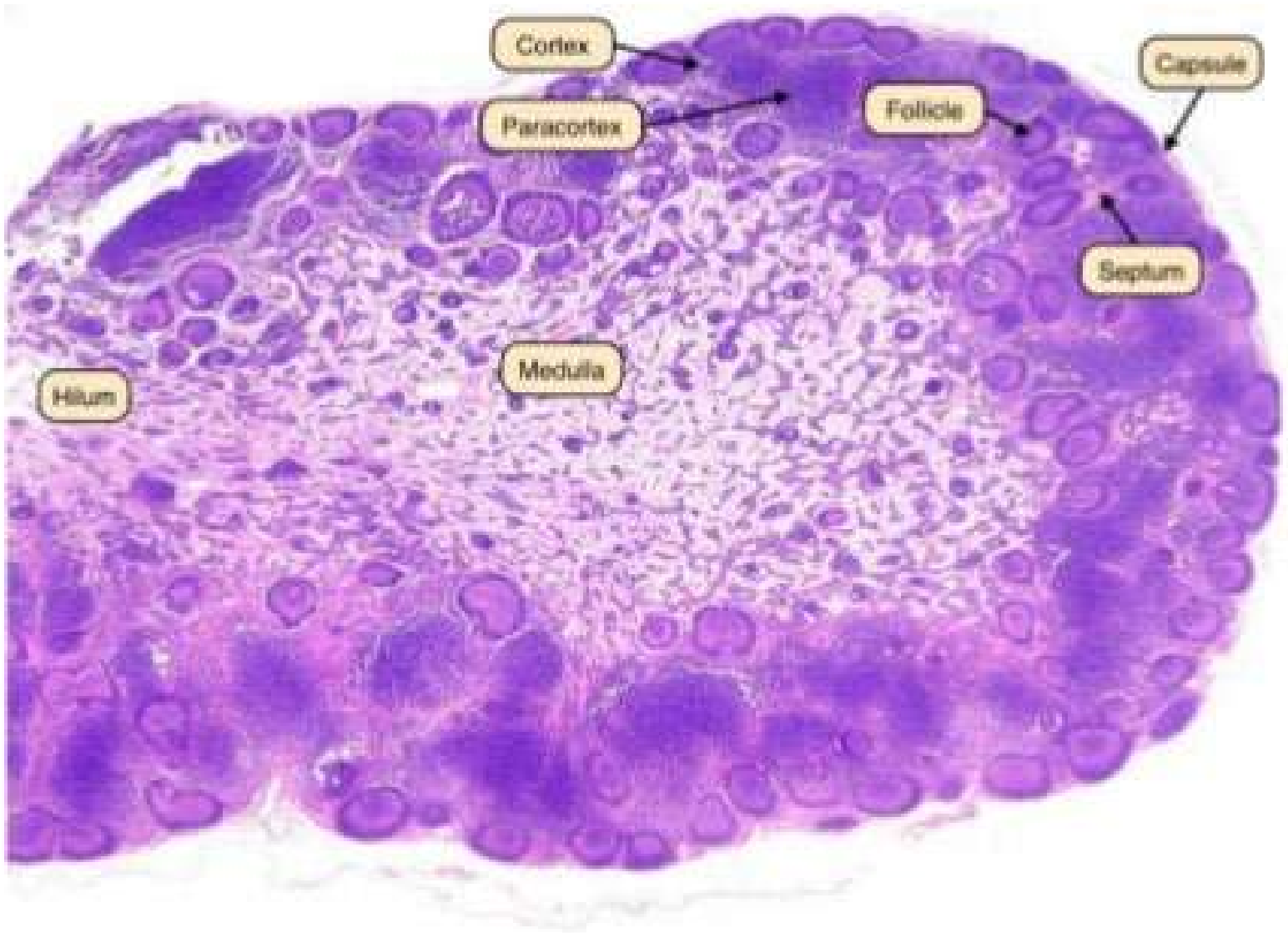


[1] Mucosa-associated lymphoid tissue (MALT)- various part of the body
[2] Mucous membrane of intestines
[3] Peyer's patches (ileum)

Lymph Node

Lymph nodes are small glands that filter lymph, the clear fluid that circulates through the lymphatic system. They become swollen in response to infection and tumors.



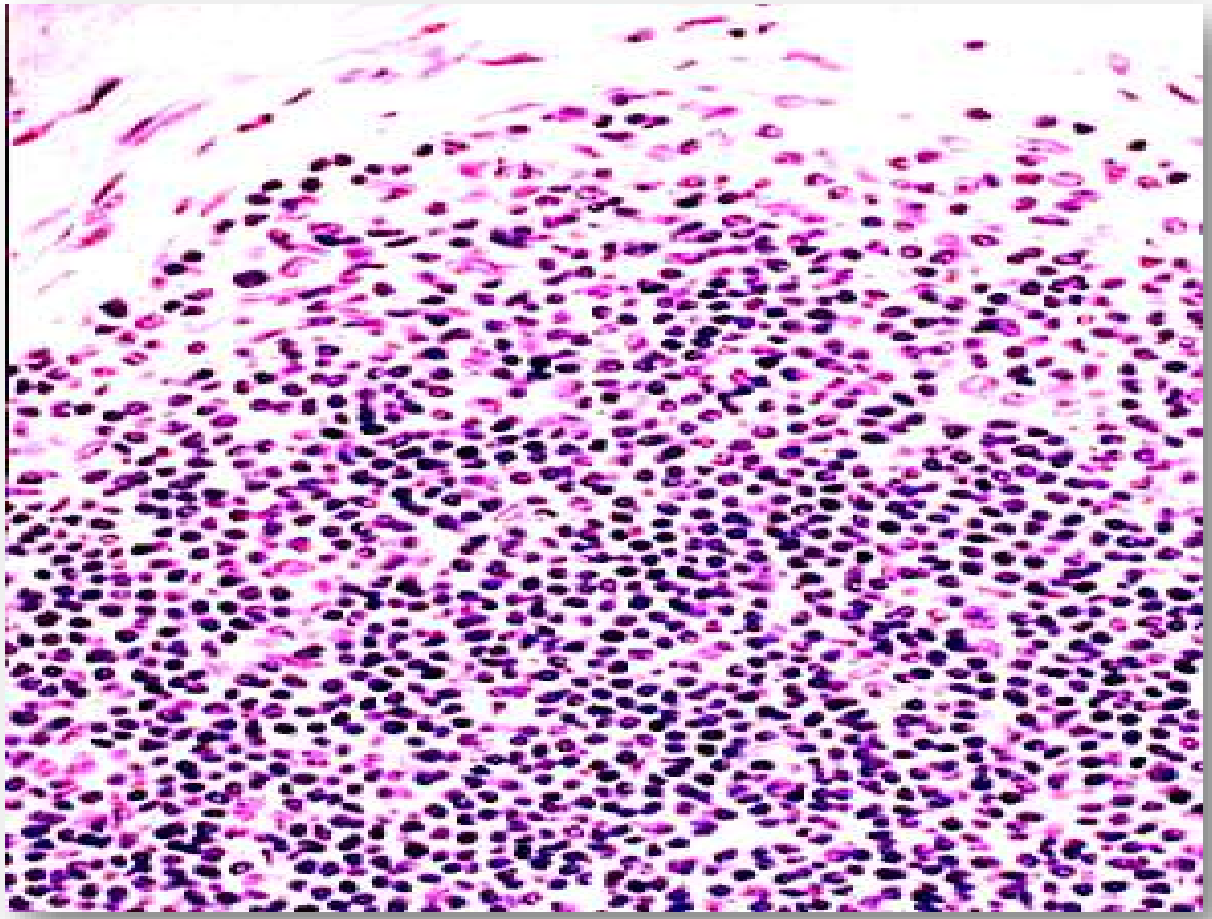

Cortex
Capsule
Paracortex
Follicle
Septum
Medulla
Hilum

The lymph node consist of a cortex which contains the primary and secondary lymphoid follicles

In the absence of immune stimulation, the cortical lymphoid follicles are **primary follicles**, composed of small B lymphocytes.

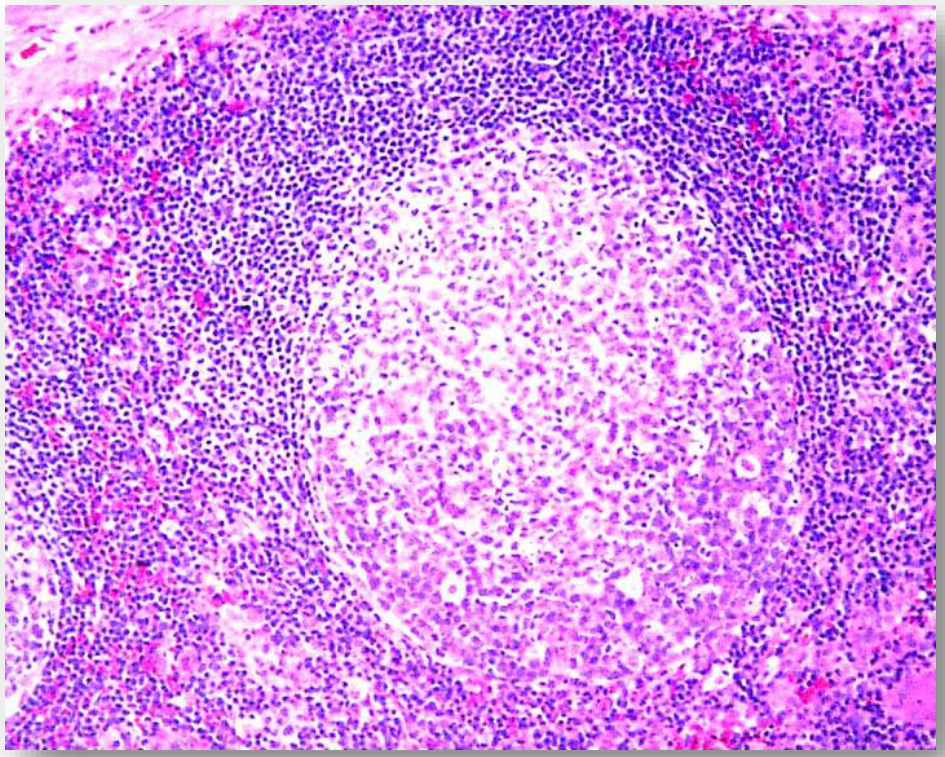
With antigenic stimulation, antigen recognizing B cells are stimulated to replication and differentiation. This converts the primary follicle into a **secondary follicles** or germinal center surrounded by a **mantle zone (MZ)** of transient small lymphocytes, and a central area containing replicating "follicular center cells" and their differentiating progeny.

Primary follicles are microscopic aggregates of naive small B lymphocytes, which express pan B-cell markers.



The formation of **secondary follicles**, including germinal centers, starts with antigen presentation by follicular dendritic cells. On antigen encounter, naive B lymphocytes undergo transformation, proliferation and differentiation into precursors of antibody-producing plasma cells and memory B cells .

The remaining naive B cells are displaced into the periphery of the germinal center and form the mantle zone.



❖ Cytology of the lymph node

The lymph node is a dynamic organ, composed of B and T lymphocytes and their subgroups. These cells are cytologically unique, and others are cytologically indistinguishable.

Examples of the cell types; small lymphocytes, follicular cells, immunoblast and the accessory cells.

1. Small lymphocytes; small round dark blue cells, with round nucleus, clumped chromatin, small or absent nucleolus.

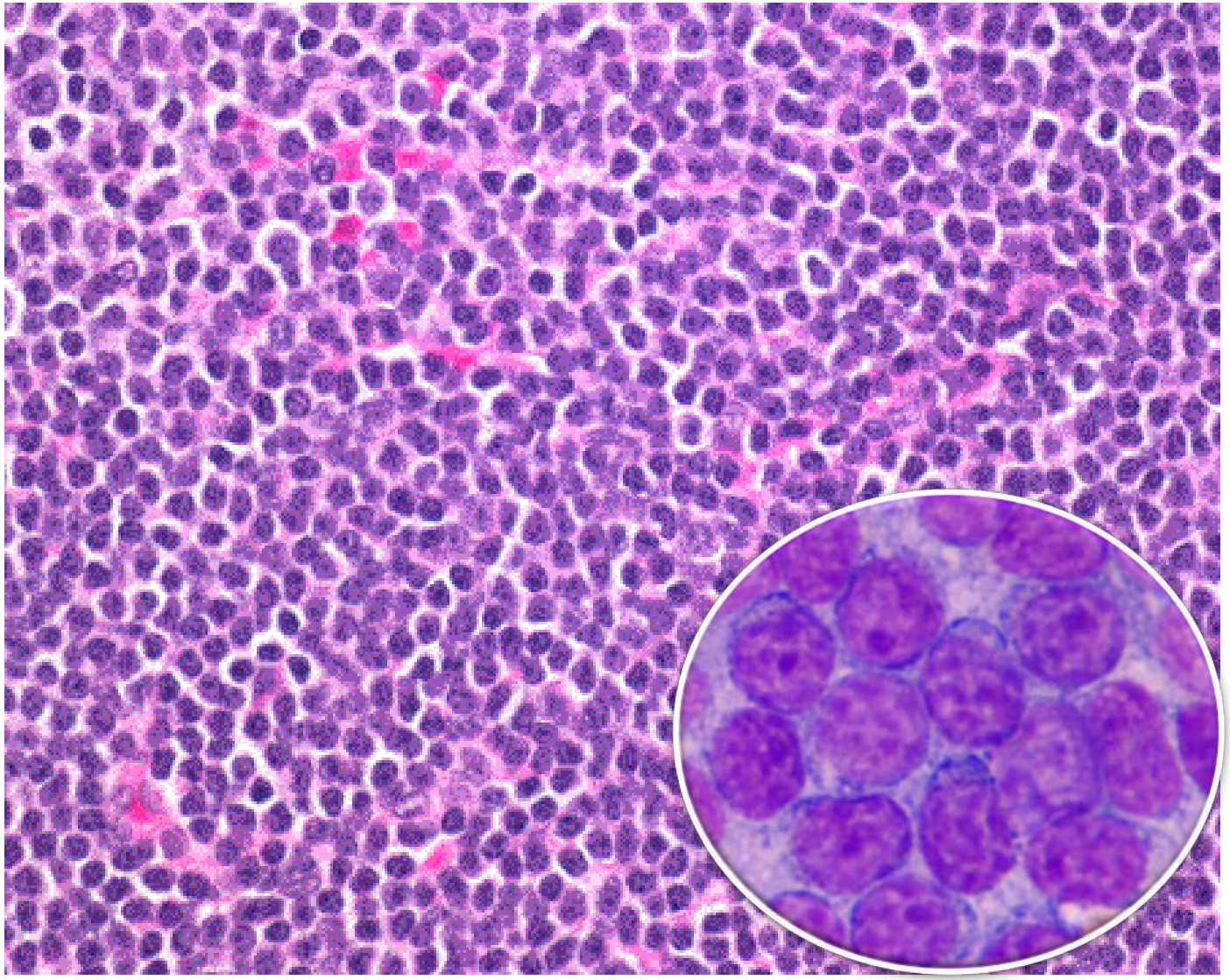
2. Immunoblasts; proliferating large cells found outside the germinal centers. May be of B or T cell type, with vesicular chromatin and nucleoli.

3. Follicular (germinal) center cells; either large or small cleaved or noncleaved cells depending on the cell size and nuclear outline morphology. The cleaved cell usually with irregular nuclear outline, while the noncleaved shows a smooth nuclear outline.

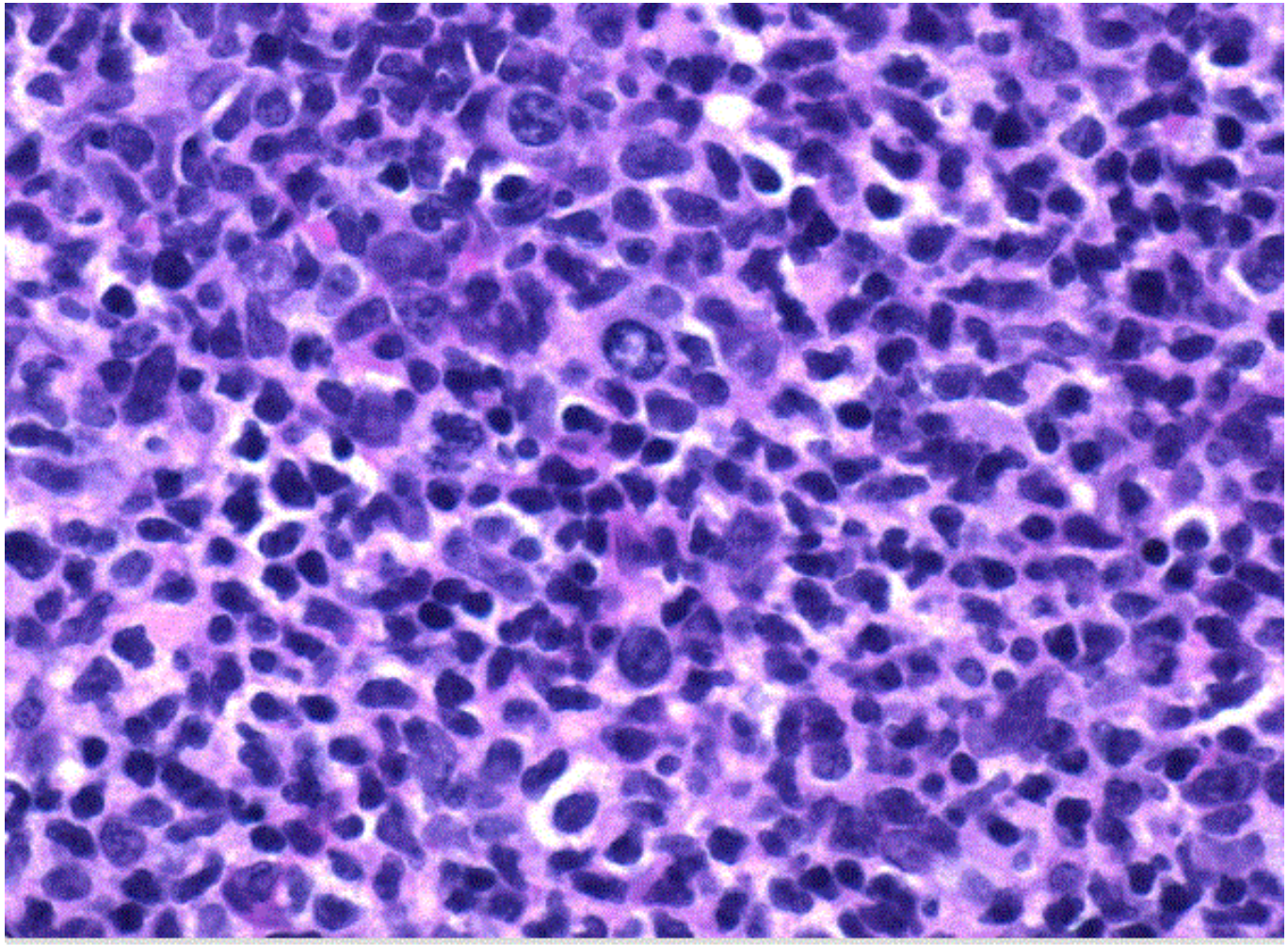
4. Accessory cells;

a. Antigen processing cells; which process and present antigen to B and T lymphocytes. Its invisible in normal lymph node.

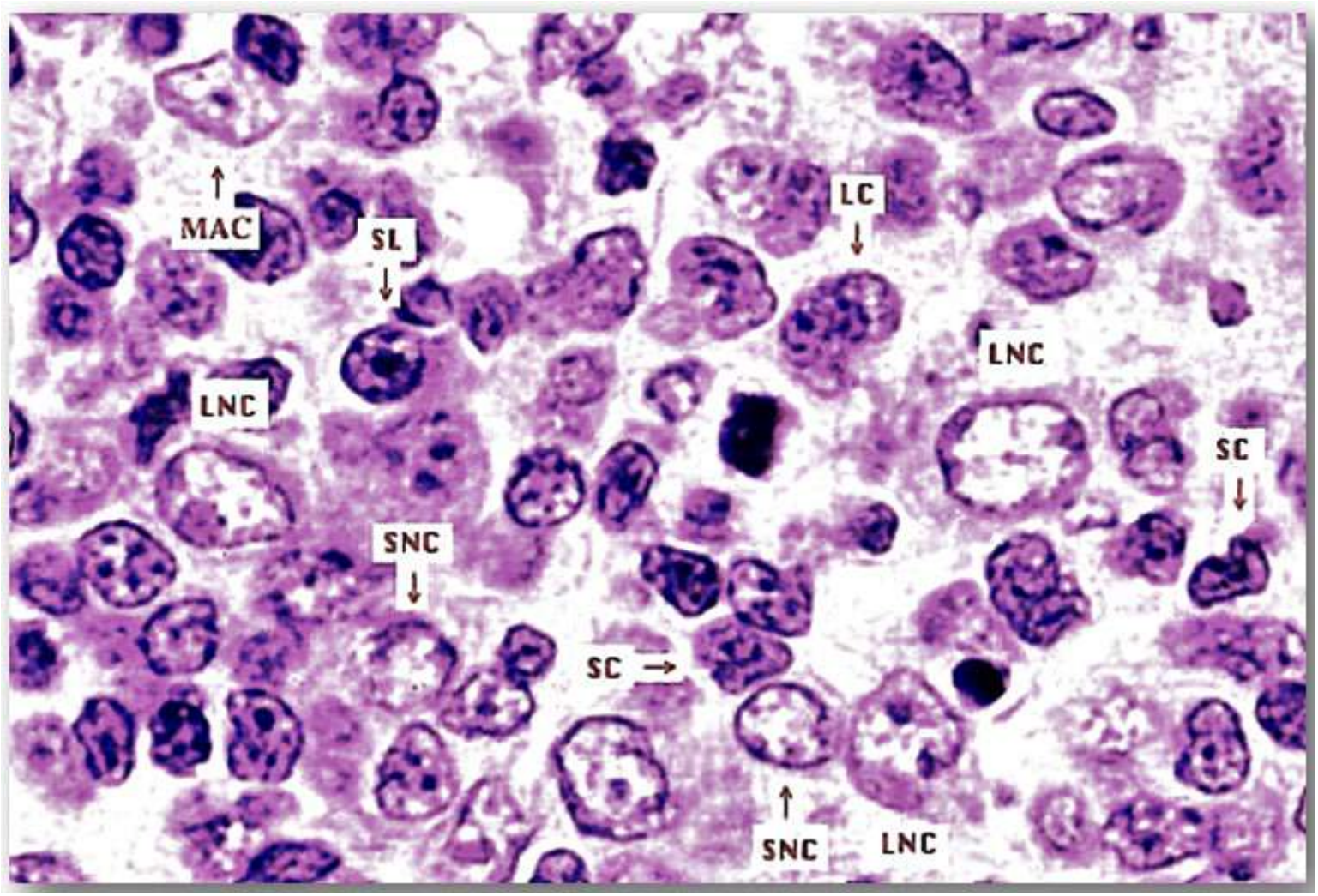
b. Macrophages (histiocytes); macrophages of germinal centers with abundant pale cytoplasm, oval nucleus and small nucleolus.



Small lymphocyte; small cell with scant amount of basophilic cytoplasm and round nucleus with clumped chromatin pattern and no nucleoli



Small and large cleaved lymphocyte; heterogenous cells with irregular nuclear outline.



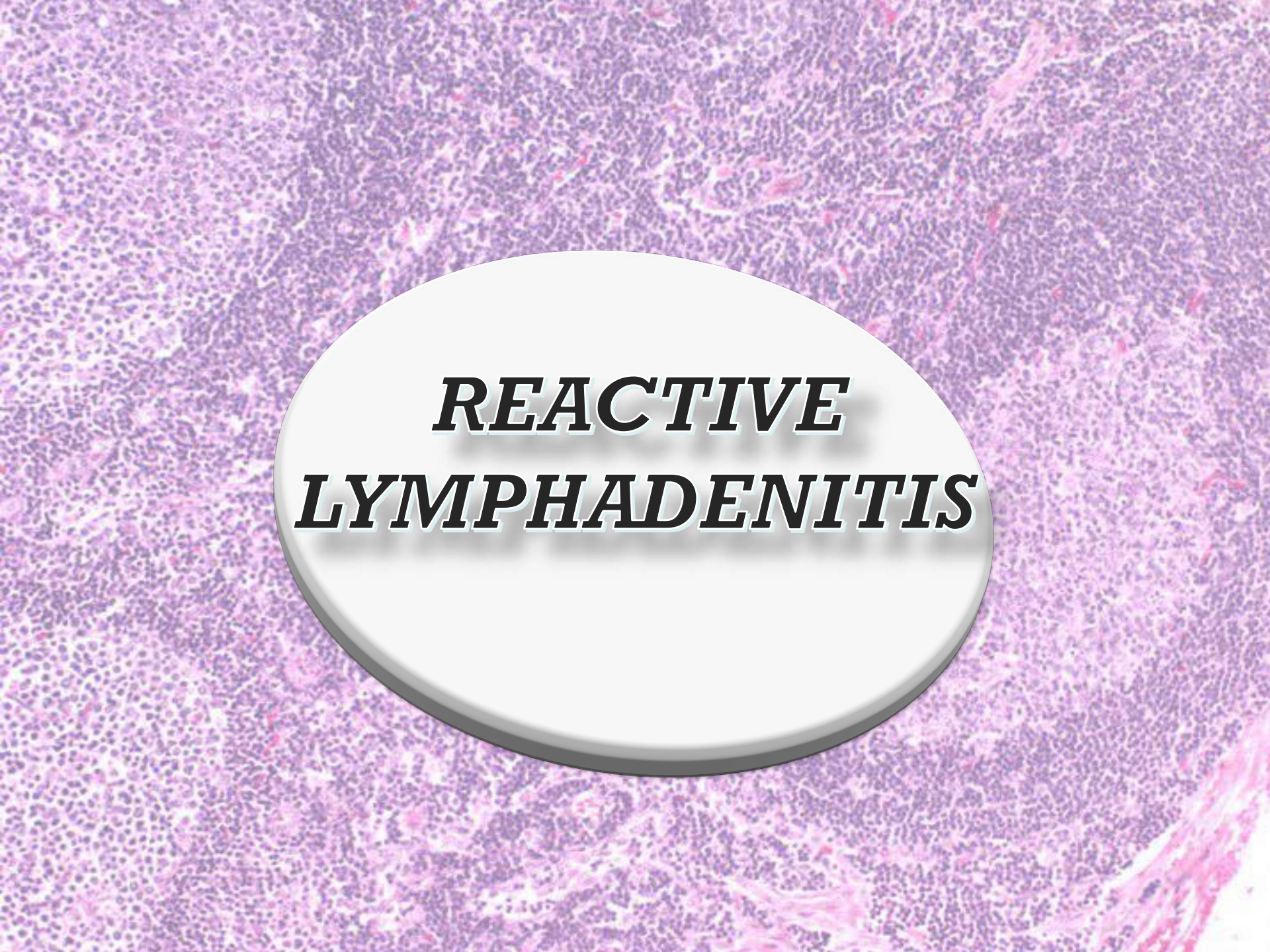
SL; small lymphocyte, SC; small cleaved, SNC; small non-cleaved, LC; large cleaved, LNC; large non-cleaved

Disorders of Lymphoid Tissue

1- Reactive (non- neoplastic) conditions; enlargement of the entire lymph node, or selective expansion of cortical, paracortical or medullary regions.

Either acute or chronic.

2- Neoplastic lesions; which can be primary lymphoid neoplasm or metastatic.


REACTIVE
LYMPHADENITIS

1- Reactive (non- neoplastic) conditions

a- Acute non-specific Lymphadenitis
b- Chronic non-specific lymphadenitis
c- Chronic granulomatous inflammation

Any immune response against foreign antigens (infectious and noninfectious inflammatory stimuli) is often associated with lymph node enlargement (**lymphadenopathy**).

The infections of the LN lead to lymphadenitis which may be acute or chronic.

In most instances, the histological appearance of the nodes is entirely nonspecific. i.e. different causes are associated with similar microscopic changes.

a- Acute nonspecific Lymphadenitis:

The affected nodes are tender, and become fluctuant when abscess is formed. The overlying skin is frequently red, which revert to their normal appearance or, if damaged undergo fibrosis.

Grossly: inflamed nodes are swollen and gray-red.

Microscopically:

- Large germinal centers containing numerous mitosis.

-When the cause is a **pyogenic** organism, a neutrophilic infiltrate is seen about the follicles and within the lymphoid sinuses. With severe infections, the centers of follicles can undergo **suppurative necrosis.**

b- Chronic Nonspecific Lymphadenitis

Three patterns, depending on the causative agent:

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

1- Follicular Hyperplasia

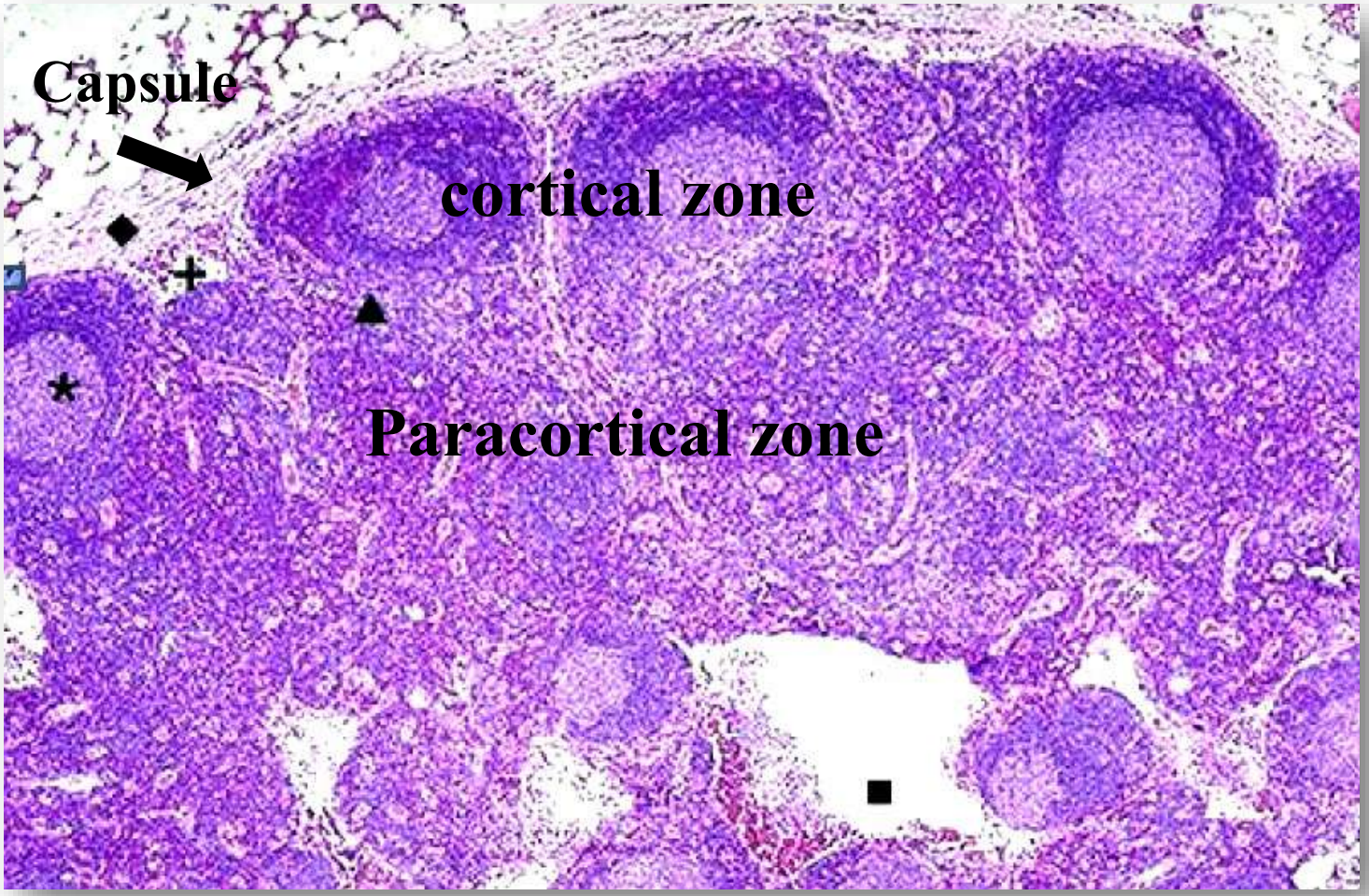
Associated with infections or inflammatory processes that activate B cells in the follicles, and thus create the follicular (or germinal center) reaction.

- The cells in the reactive follicles include the **activated** B cells (centrocytes and centroblasts also called follicular center cells.

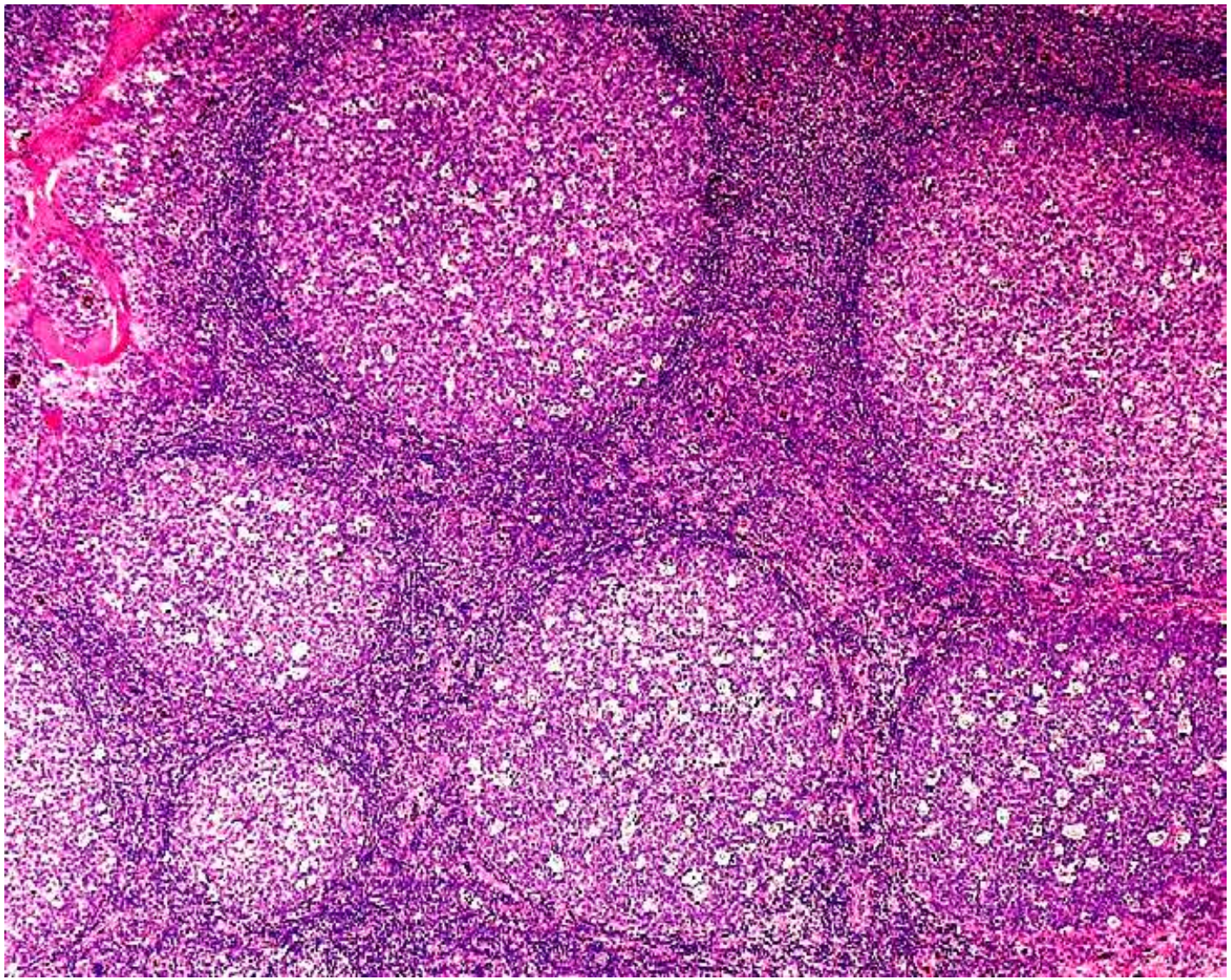
- Scattered phagocytic macrophages containing nuclear debris forming **tingible body macrophage** predominantly in germinal centers, containing many phagocytized, apoptotic cells in various states of degradation, referred to as tingible bodies (tingible meaning stainable).

- **Causes;** of follicular hyperplasia include rheumatoid arthritis, toxoplasmosis, and the early stages of HIV infection.

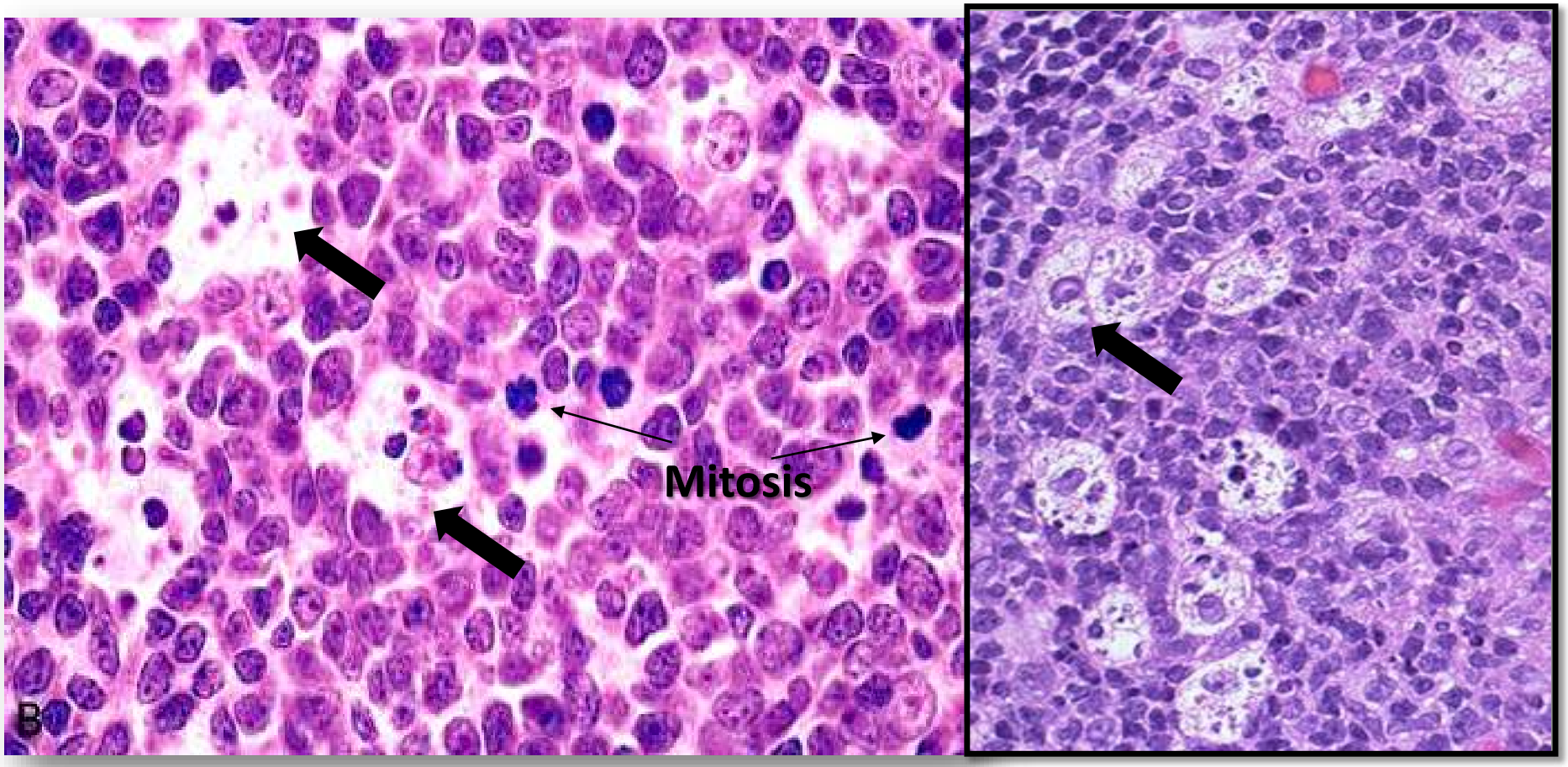
- This form of lymphadenitis can be **confused** with follicular lymphomas microscopically.



Benign reactive lymph node; the lymphoid follicles, consists of a pale germinal centre surrounded by a dark blue mantle (cuff) of small, mature lymphocytes.



Reactive follicular hyperplasia with numerous secondary follicles scattered throughout the lymph node.



High-power; shows several mitotic figures and numerous macrophages containing phagocytosed apoptotic cells (tingible bodies, arrow). Presence of frequent mitotic figures, phagocytic macrophages, all of which tend to be absent from neoplastic follicles.

2-Paracortical Hyperplasia;

The **paracortex** is the zone situated between the cortex and the medulla, which contains the mobile pool of T-lymphocytes responsible for cell-mediated immune responses.

- Characterized by reactive changes within the T-cell regions of the lymph node.

- On immune activation parafollicular T-cells transform into large proliferating immunoblasts.

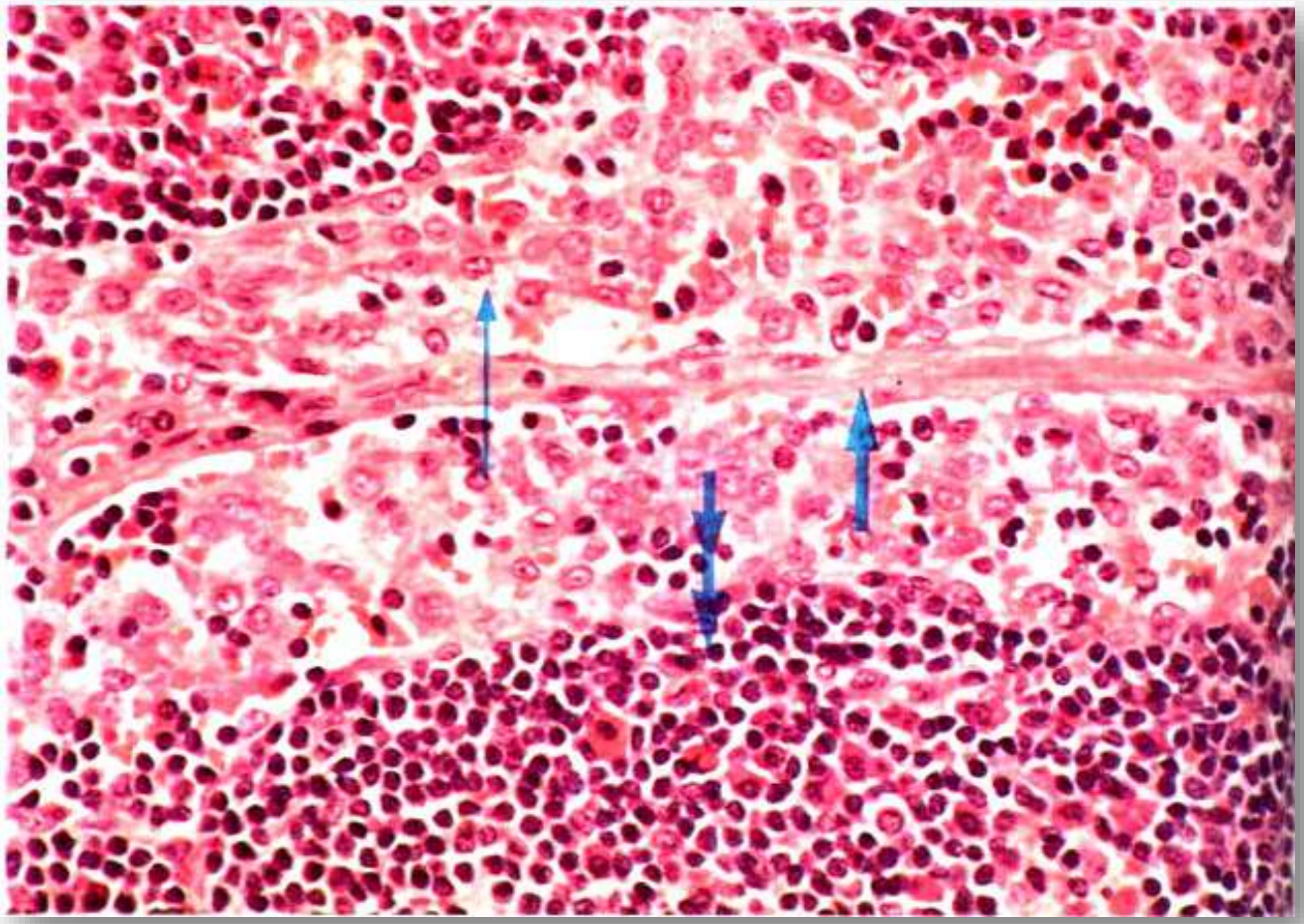
- Paracortical hyperplasia is encountered in:

Viral infections (such as EBV), following certain vaccinations (e.g., smallpox) and in immune reactions induced by certain drugs.

3- Sinus Histiocytosis;

- Characterized by distention and prominence of the lymphatic sinusoids, owing to a marked hypertrophy of lining endothelial cells and an infiltrate of macrophages.

- Sinus histiocytosis is often encountered in lymph nodes draining cancers and may represent an immune response to the tumor or its products.



Lymphatic sinusoids, are greatly distended, and their lumens are filled with large numbers of large eosinophilic histiocyte-like cells (thin arrows). Fibro muscular septa (thick arrows), which divide each sinus into twin channels, can be seen. The medullary lymphoid tissue (double arrow) consists of small lymphocytes, plasma cells and histiocytes.

C- Chronic Granulomatous Lymphadenitis:

The **Granuloma** means a collection of macrophages due to inflammation. The causes of granulomatous lymphadenitis include, infections, foreign body reactions and malignancy.

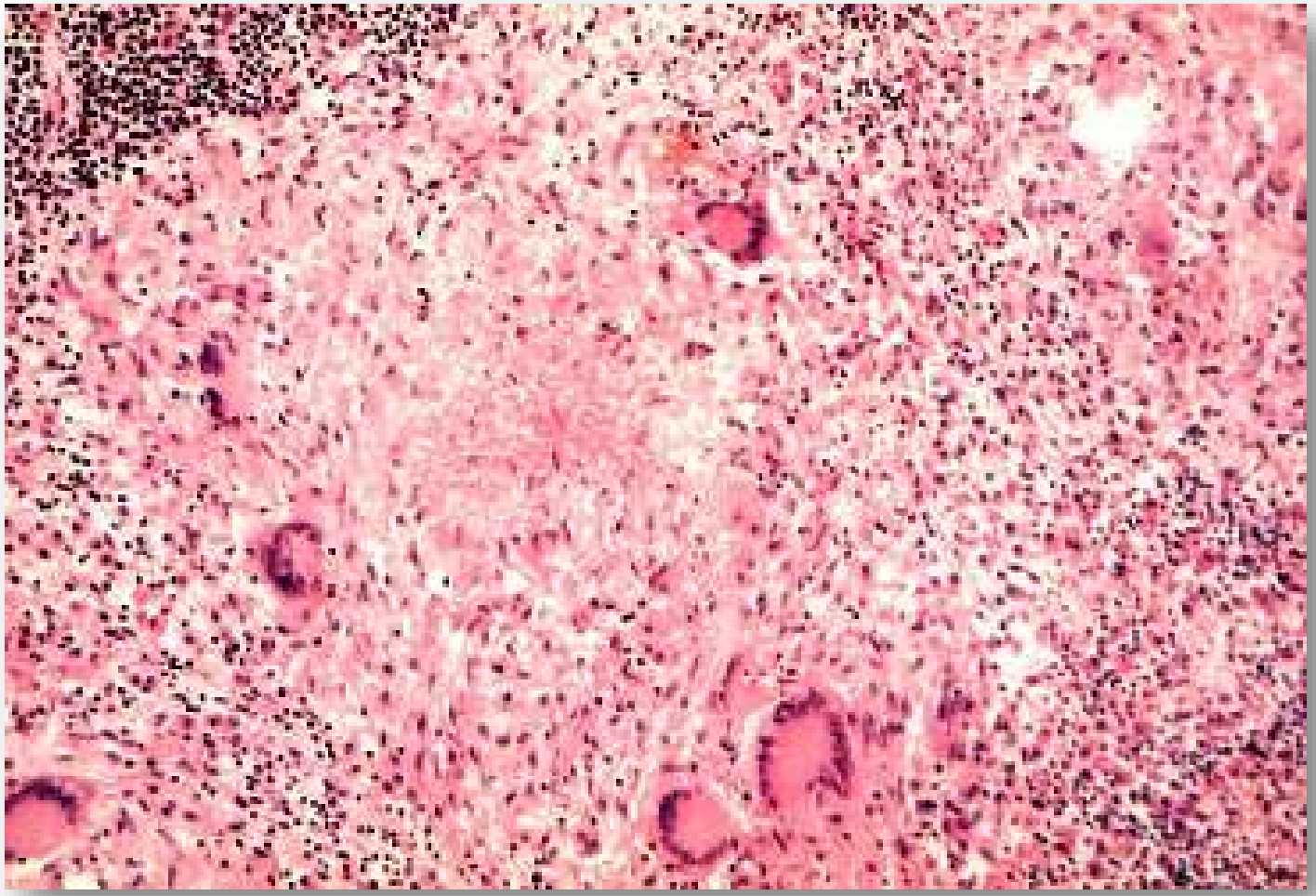
- Among the infectious causes are: Tuberculosis, Atypical mycobacteriosis, Sarcoidosis, Fungal infections, Syphilis, Toxoplasmosis and Leprosy.

- Malignancy related granulomatous lymphadenitis;

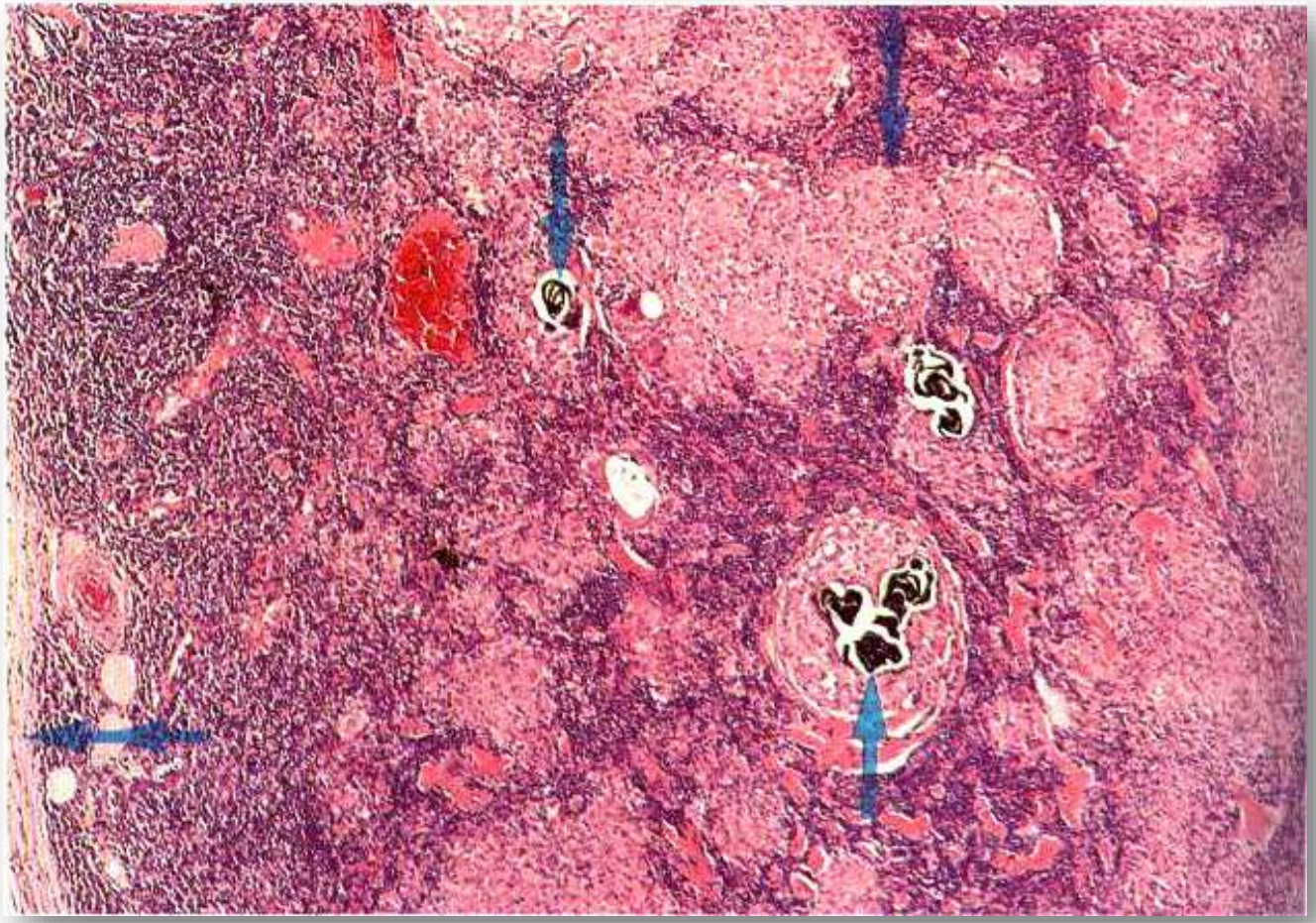
  - Primary (Hodgkin & non-Hodgkin lymphomas), or

  - Secondary (metastatic carcinoma). It occurs whether the node is involved by the malignancy or not.

Sometimes the appearance of **Caseating Granuloma** means necrosis involving dead cells with no nuclei and debris. Grossly appear as cheese like pattern that a specific diagnosis can be strongly suggested.



Tuberculosis; presence of caseous necrosis; Langerhans giant cells.



Sarcoidosis; There are numerous round eosinophilic (sarcoid) follicles (arrow), consisting of epithelioid histiocytes, scattered throughout the blue-staining lymphoid tissue beneath the capsule (double arrow). There is no necrosis within the follicles, but some contain laminated black (calcified) Schaumann bodies (thick arrows)

LYMPHOID NEOPLASIA

Lymphoid Neoplasms

A group of monoclonal disorders originate from a single transformed cell of lymphoid origin, immune system cells.

These malignancies include; leukemias, lymphomas, and plasma cell dyscrasias.

- All these have the potential to spread to lymph nodes and various tissues throughout the body, especially the liver, spleen, and bone marrow.

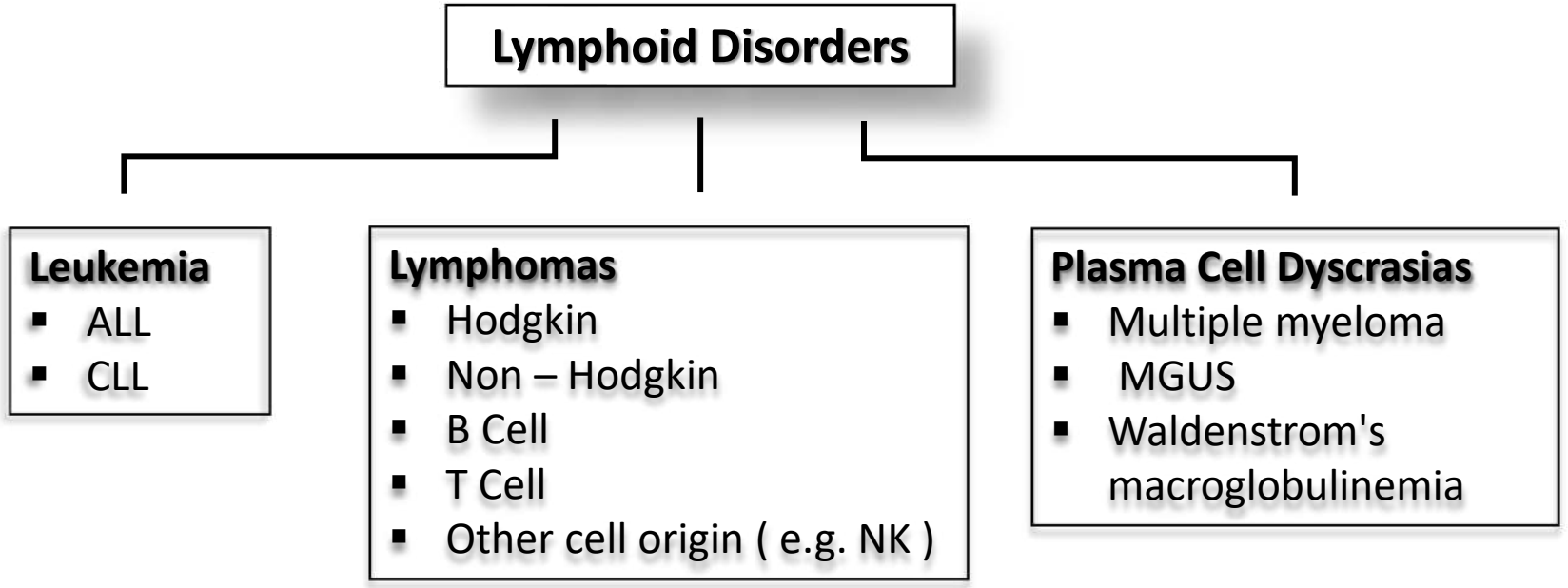
- In some cases lymphomas spill over into the peripheral blood, creating a leukemia-like picture **(leukemic phase)**.

- Conversely, leukemias of lymphoid cells, originating in the bone marrow, can infiltrate lymph nodes and other tissues, creating the histological picture of **lymphoma**.

Leukemia; is used for neoplasms that present with widespread involvement of the bone marrow and (usually, but not always) the peripheral blood.

Lymphoma; is used for proliferations that arise as discrete tissue masses, without involvement of the peripheral blood.

There is an overlapping between these 2 entities.



ALL; Acute Lymphoblastic Leukemia, CLL; Chronic LL, MGUS; monoclonal gammopathy of unknown significance

Infections associated with hemopoietic malignancies

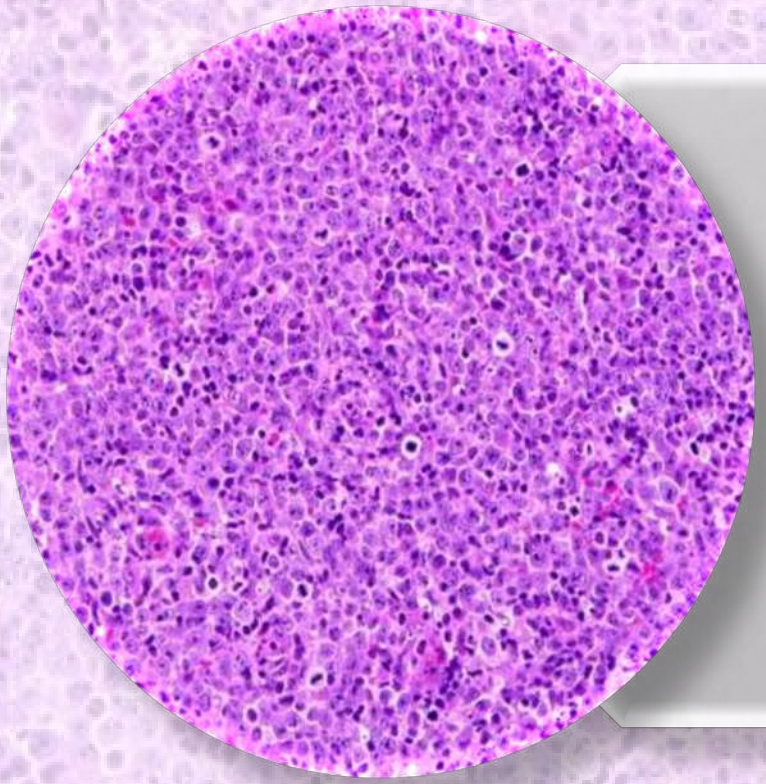
Infection	Tumour
1- Virus;	
HTLV-1	Adult T-cell leukemia/lymphoma
Epstein-Barr virus (EBV)	Burkitt and Hodgkin lymphomas, PTLD
HHV-8	Primary effusion lymphoma, multicentric Castleman's disease,
HIV-1	High-grade B-cell lymphoma, primary CNS lymphoma, Hodgkin lymphoma
Hepatitis C	Marginal zone lymphoma
2- Bacteria; H.pylori	Gastric lymphoma (MALT)
3- Protozoa; Malaria	Burkitt lymphoma

HHV-8; human herpes virus 8, HIV; human immunodeficiency virus, HTLV-1; human T-lymphotropic virus type 1, MALT; mucosa-associated lymphoid tissue, PTLD; post-transplant lymphoproliferative disease

The WHO Classification of the Lymphoid Neoplasms

Five broad categories, which are separated according to the cell of origin:

I.	Precursor B-cell neoplasms (Neoplasms of immature B cells)
II.	Peripheral B-cell neoplasms (Neoplasms of mature B cells)
III.	Precursor T-cell neoplasms (Neoplasms of immature T cells)
IV.	Peripheral T-cell and NK-cell neoplasms (Neoplasms of mature T cells and NK cells)
V.	Hodgkin lymphoma (Neoplasms of Reed-Sternberg cells and variants)



NON-HODGKIN LYMPHOMA

Classification of Lymphoid Neoplasms

Many classification systems were developed; Rappaport classification (1966), Kiel classification (1974), Lukes and Collins classification (1974),Working formulation for clinical usage (1982), REAL classification (1994) and WHO classification (2008) and revised (2016).

The current World Health Organization (WHO) classification scheme uses:

- Morphologic,
- Immunophenotypic,
- Genotypic, and
- Clinical features .

Working Formulation for Clinical Usage

I. Low Grade

A. Small lymphocytic lymphoma

B. Follicular predominantly small cleaved cell lymphoma

C. Follicular mixed small cleaved and large cell lymphoma

II. Intermediate Grade

D. Follicular predominantly large cell lymphoma.

E. Diffuse small cleaved cell lymphoma.

F. Diffuse mixed small and large cell lymphoma.

G. Diffuse large cell lymphoma.

III. High Grade

H. Immunoblastic lymphoma.

I. Lymphoblastic Lymphoma.

J. Small non-cleaved cells Lymphoma.

Mature B-cell neoplasms

- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic B-cell marginal zone lymphoma
- Hairy-cell leukaemia
- Splenic lymphoma/leukaemia unclassifiable
  - Splenic diffuse red pulp small B-cell lymphoma
  - Hairy-cell leukaemia variant
- Lymphoplasmacytic lymphoma/Waldenstr¨om macroglobulinemia
- Heavy-chain diseases
- Plasma-cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - Paediatric nodal marginal zone lymphoma
- Follicular lymphoma
  - Paediatric follicular lymphoma
- Primary cutaneous follicle centre lymphoma
- Mantle-cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
  - T-cell/histiocyte-rich LBCL
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - EBV-positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphomas arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukaemia
Systemic EBV-positive T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell leukaemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
S´ezary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8-positive aggressive epidermotropic
cytotoxic T-cell lymphoma
Primary cutaneous CD4-positive small/medium T-cell lymphoma
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, ALK positive
Anaplastic large-cell lymphoma, ALK negative
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

Malignant Lymphoma Staging

- Inspection of the Waldeyer ring is particularly important.

- Bone marrow biopsy should be performed in all patients.

- Radiography,

- Computed tomography (CT),

- Magnetic resonance imaging (MRI) or positron emission tomography (PET)

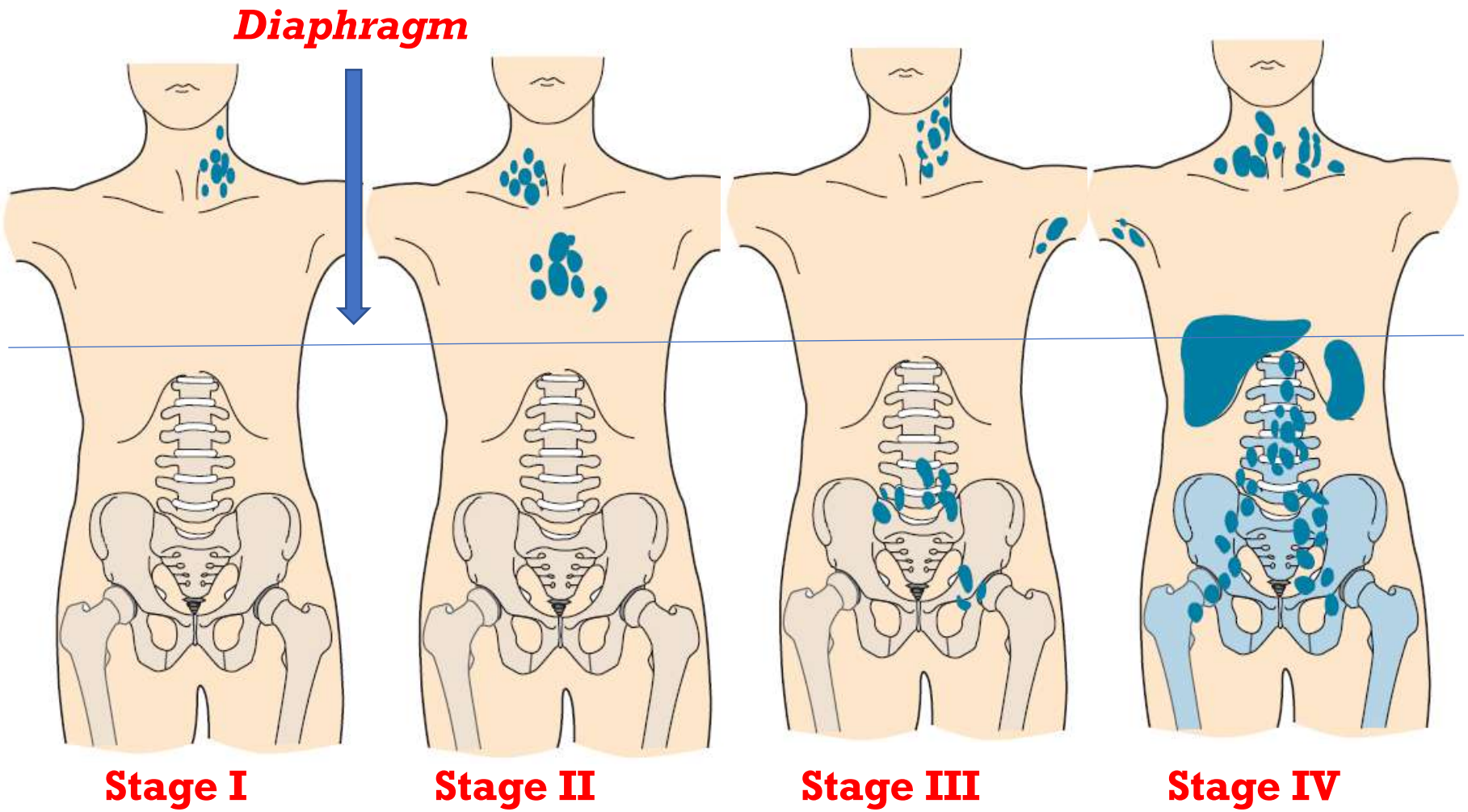
Are used for:

* initial staging of the disease and are of value in monitoring response to therapy and

* detection of minimal residual disease (MRD)or relapse.

Ann Arbor Staging System

Stage I	Involvement in a **single lymph** node region or lymphoid structure (i.e; spleen, thymus, Waldeyer's ring, appendix and Peyer's patches)
Stage II	Involvement of **2 or more lymph** node regions on the **same side** of the diaphragm. localized contiguous involvement of only one extralymphatic site and lymph node region (stage IIE)
Stage III	Involvement of lymph node regions on **both sides** of the diaphragm; may include spleen.
Stage IV	**Disseminated** involvement of one or more extralymphatic organs (i.e; liver and bone marrow) with or without lymph node involvement



Ann Arbor Staging System

I. Neoplasms of Immature B and T cells

These are aggressive tumors, composed of immature lymphocytes (lymphoblasts), which occur predominantly in children and young adults. They are microscopically indistinguishable.

- Both pre-B and pre-T lymphoblastic lymphomas usually take on the clinical appearance of an acute lymphoblastic leukemia (ALL) at some time during their course.

Peak incidence at age of 4 years (1-10 yrs), with most of the cases being of pre-B cell origin.

- The pre-T cell tumors, which initially present as thymic tumors, are most common in adolescent males of between 15 and 20 years of age.

II. Neoplasms of Mature B cells

1- Small Lymphocytic Lymphoma

2- Follicular Lymphoma

3- Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)

4- Marginal Zone Lymphomas

5- Mantle Cell Lymphoma

6- Diffuse Large Cell Lymphoma

7- Burkitt Lymphoma

8- Hairy cell leukemia

9- Multiple myeloma / solitary plasmacytoma

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

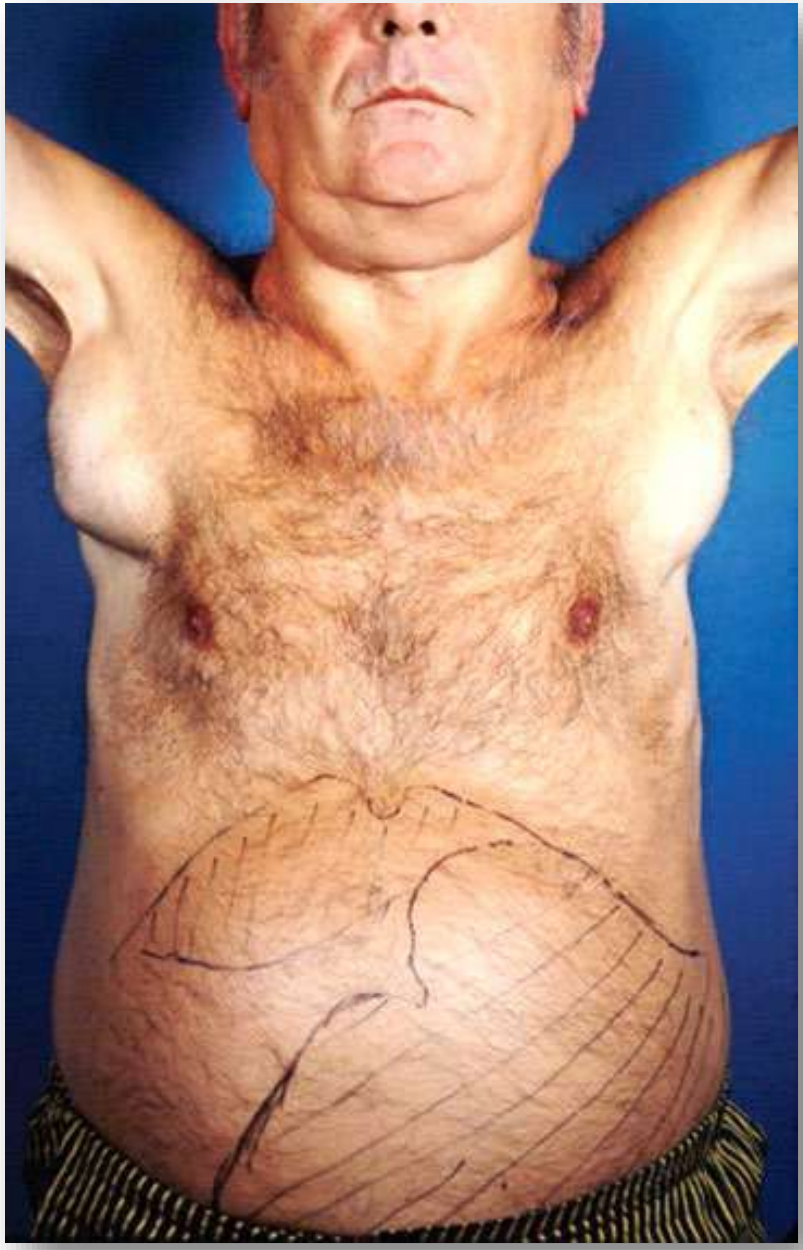
These two disorders differ only in the extent of peripheral blood involvement.

- If the peripheral blood monoclonal lymphocytosis exceeds **5000cells/mm^3**, the patient is diagnosed with **chronic lymphocytic leukemia (CLL).**
- if not, diagnosed as **small lymphocytic lymphoma (SLL)**

- In addition to the lymph nodes, the bone marrow, spleen, and liver are involved in almost all cases which associated with peripheral absolute lymphocytosis.
- Generalized lymphadenopathy and hepatosplenomegaly are present in 50% of cases.
- The median survival is about 5 years.
- **An autoimmune hemolytic anemia** appears in a bout one sixth of CLL/SLL cases .
- CLL/SLL tends to transform to more aggressive lymphoid malignancies. Once transformation occurs, the median survival drops to less than one year.

Generalized lymphadenopathy in chronic lymphocytic lymphoma/ small lymphocytic lymphoma (CLL/SLL).

Bilateral axillary lymphadenopathy and hepatosplenomegaly are present in a patient with advanced stage CLL/SLL.

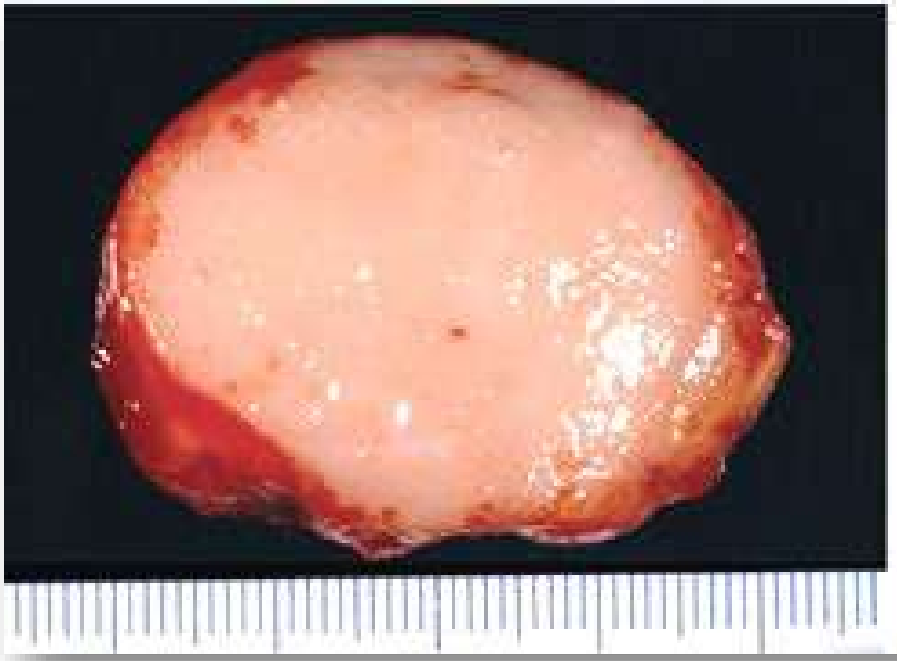


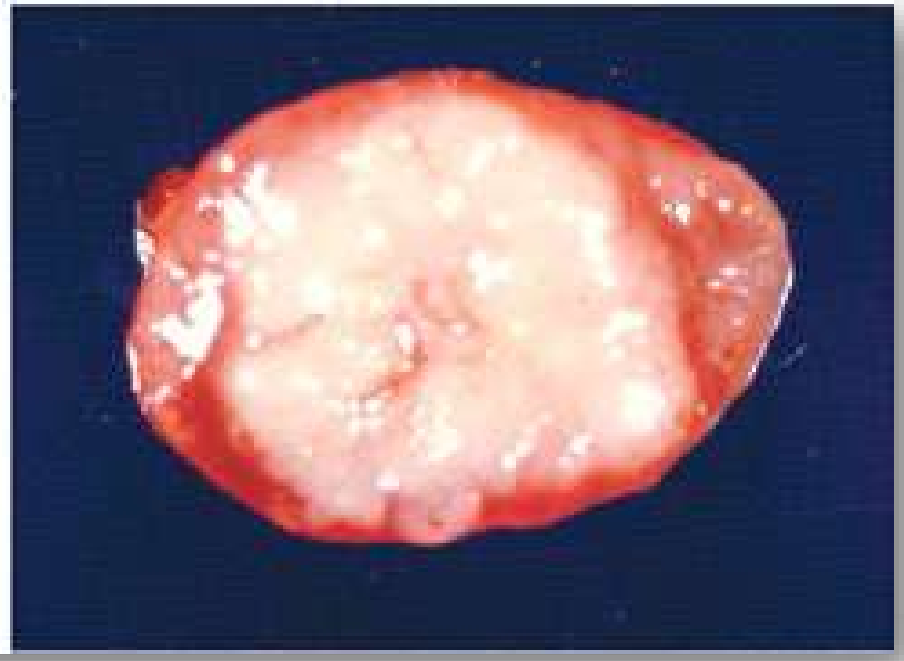
Modified Rai Staging for CLL

Staging	Lymphocytes	Lymph Nodes	Spleen	Platelet Count
0	Increased			
I	Increased	Enlarged		
II	Increased	Enlarged/some	Enlarged	
III	Increased	Enlarged/some	Enlarged	
IV	Increased			Decreased

Grossly :

Cut section of enlarged lymph nodes show characteristic homogenous pattern ("fish flesh" appearance) of a lymph node diffusely involved



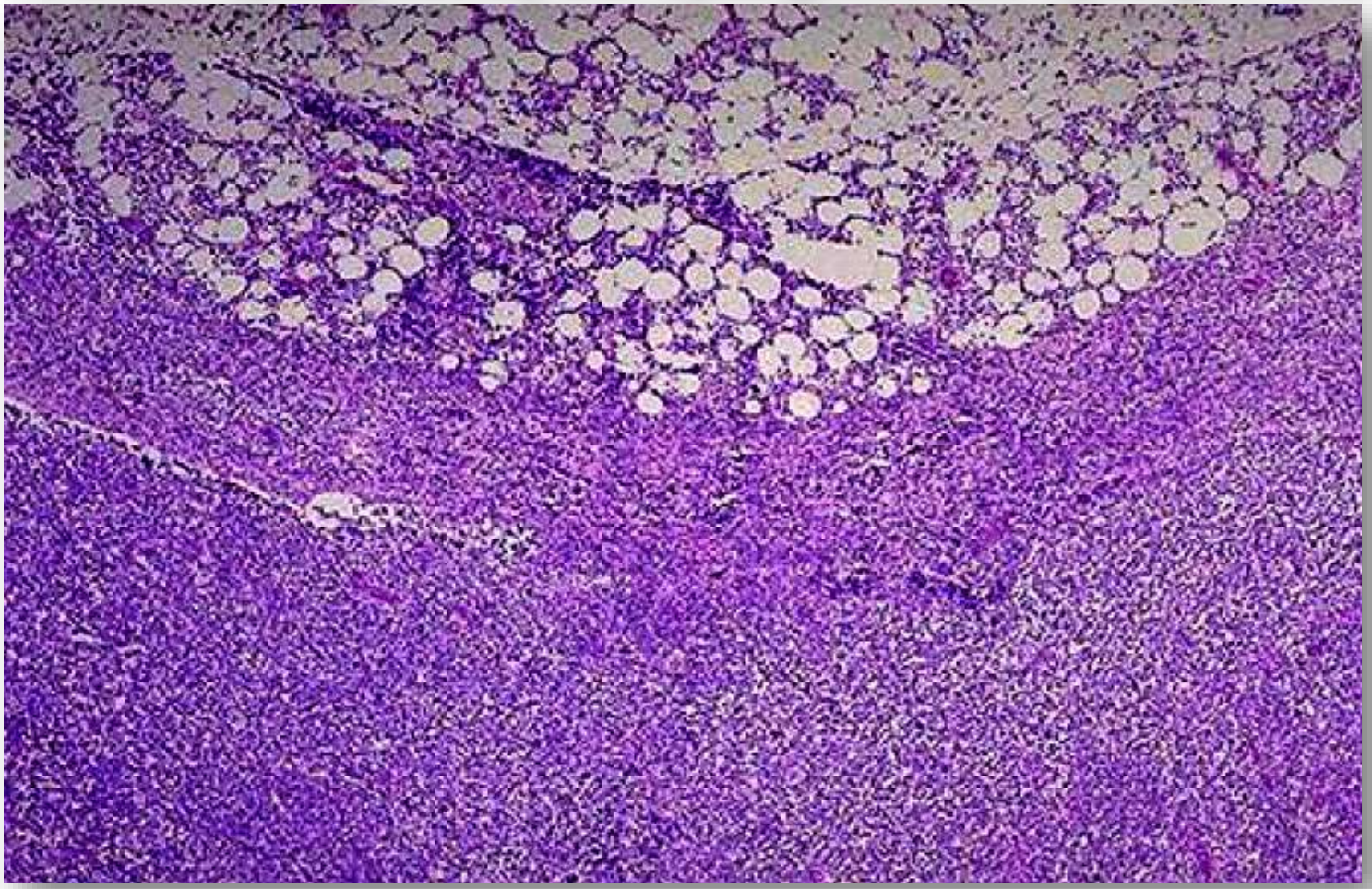


Left; characteristic homogenous pattern fish flesh appearance of a lymph node in CLL/SLL, as compared with the **right** nodular, heterogeneous appearance of a lymph node involved with metastatic cancer

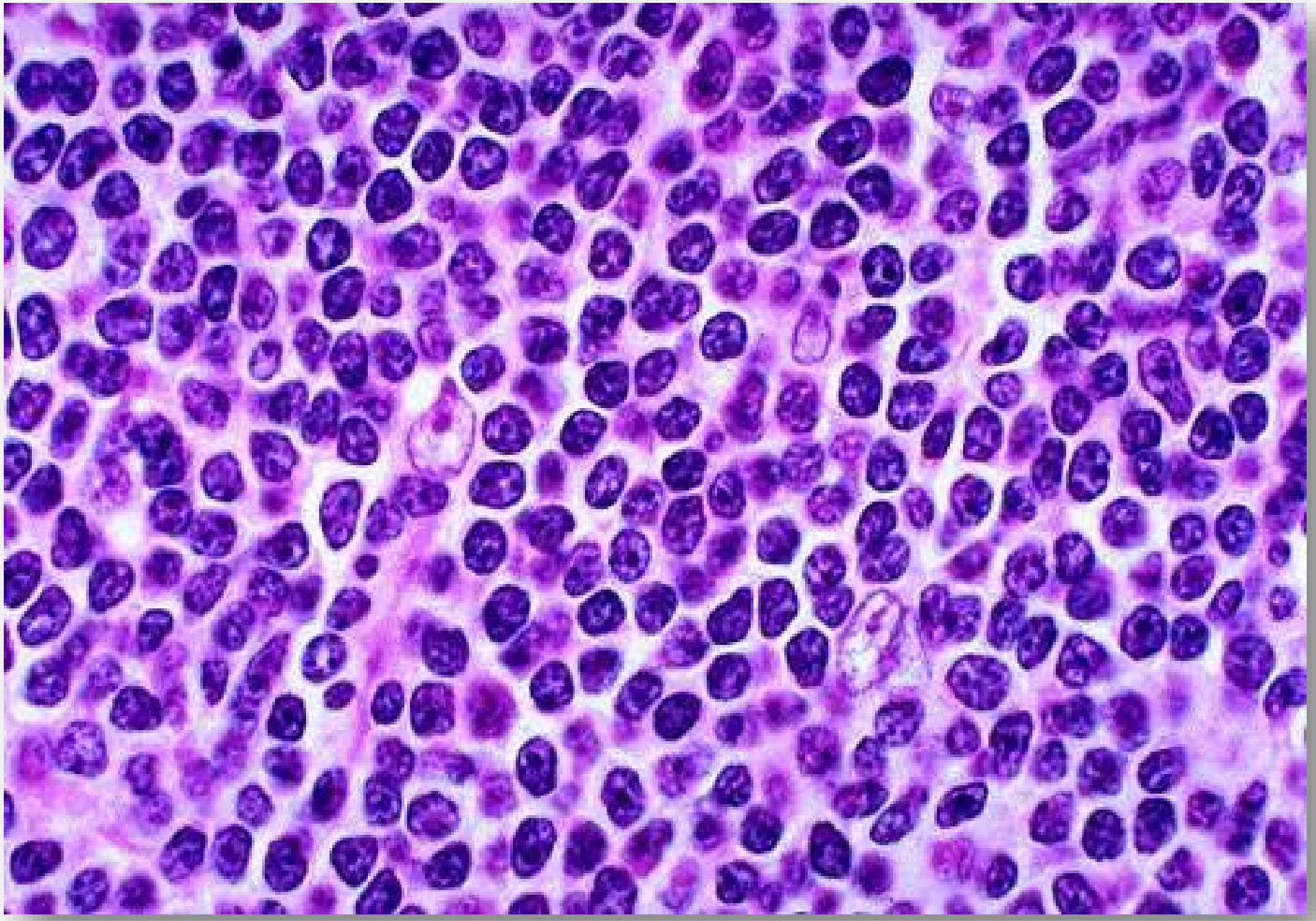
Histological features:

- There is diffuse effacement of the lymph node architecture by lymphoid cells.
- The predominant cells are monomorphic, small, resting lymphocytes with dark-staining round nuclei and scanty cytoplasm.
- CLL/SLL is a neoplasm of mature B cells **expressing pan-B cell markers.**

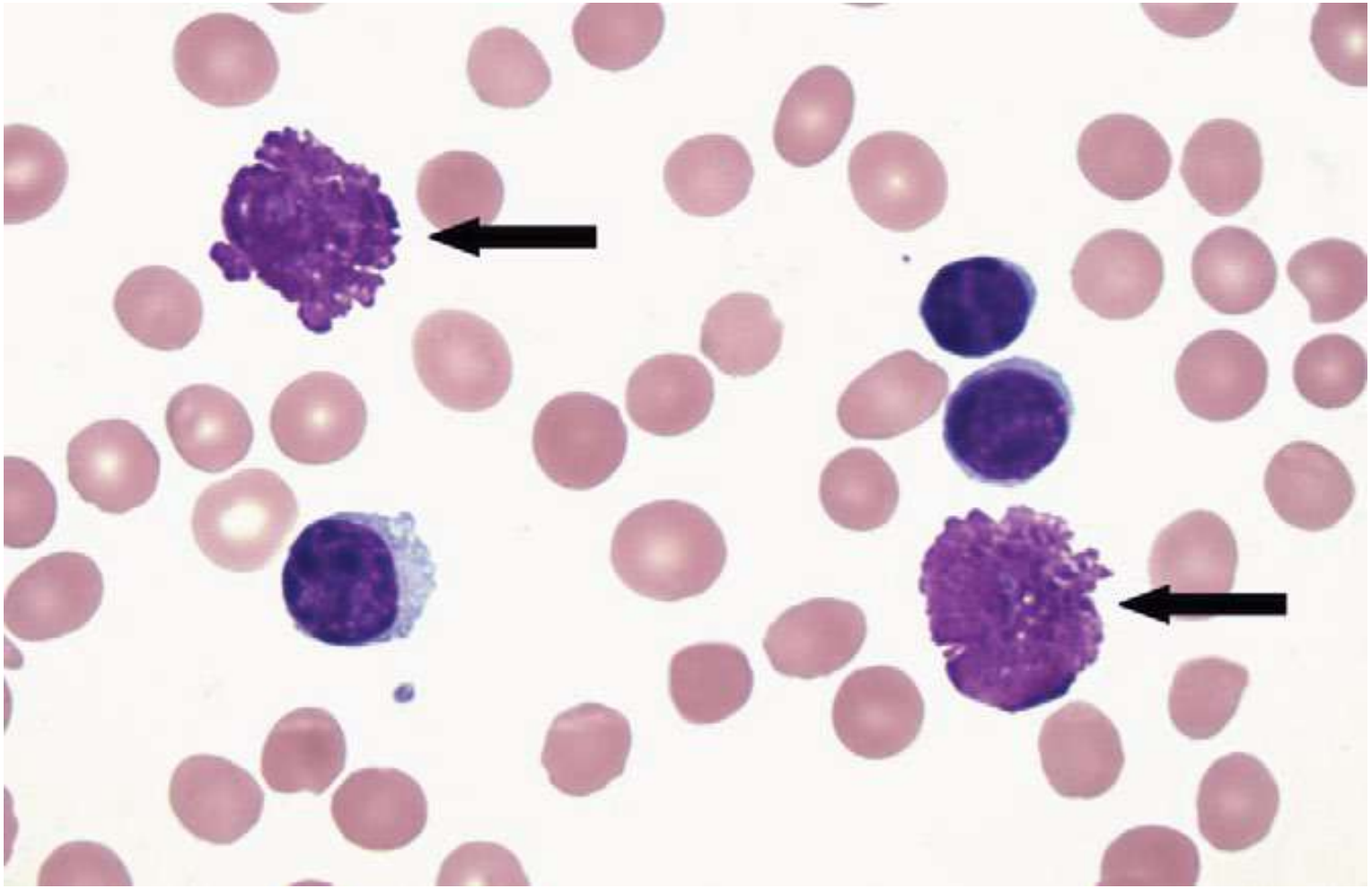
Small lymphocytic lymphoma lymph node



Low power view showing diffuse monotonous proliferation of small lymphocytes that effaces the architecture of the node (absence of follicles).



The nuclear contours are regular, the chromatin is clumped, and nucleoli are inconspicuous and scanty cytoplasm.

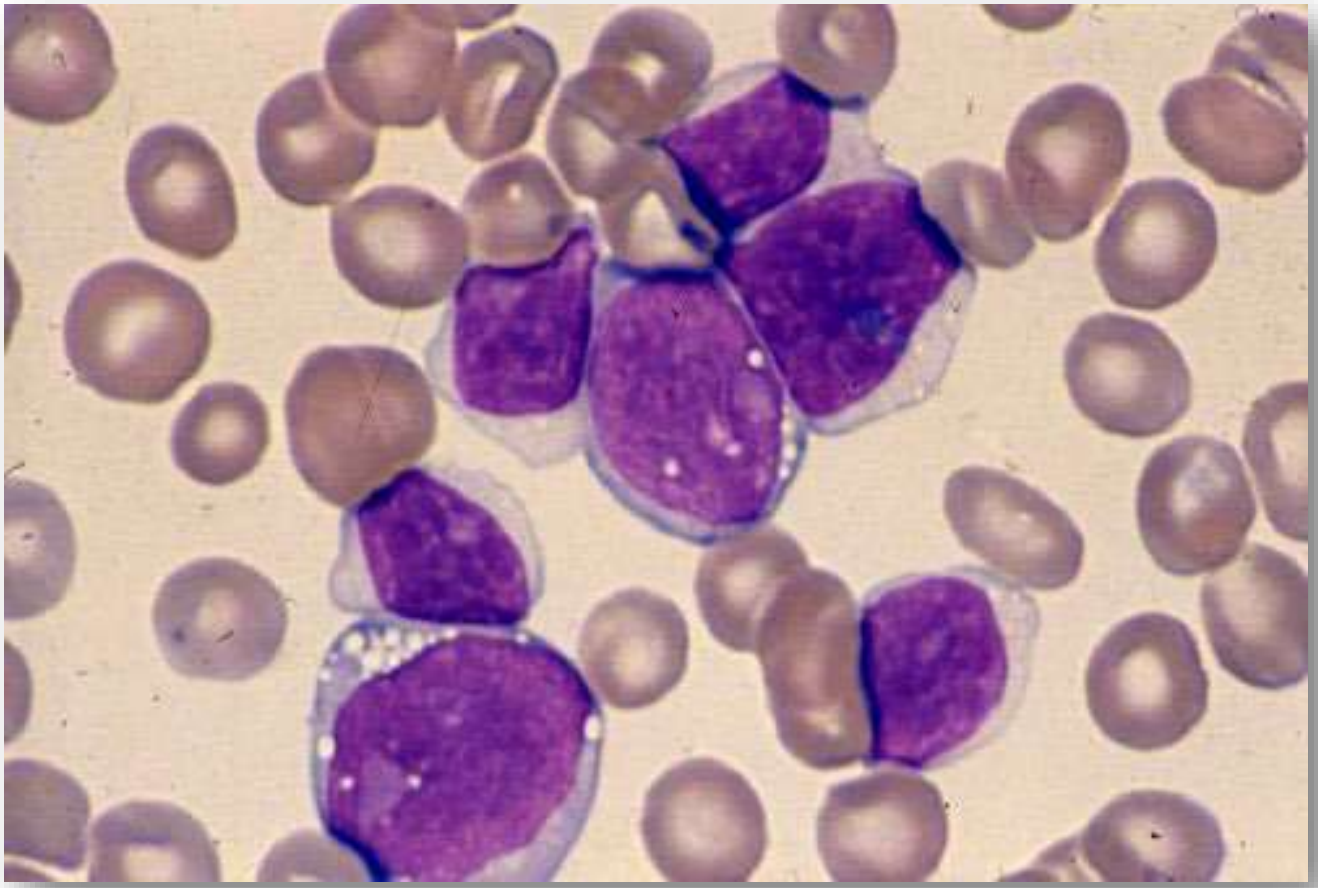


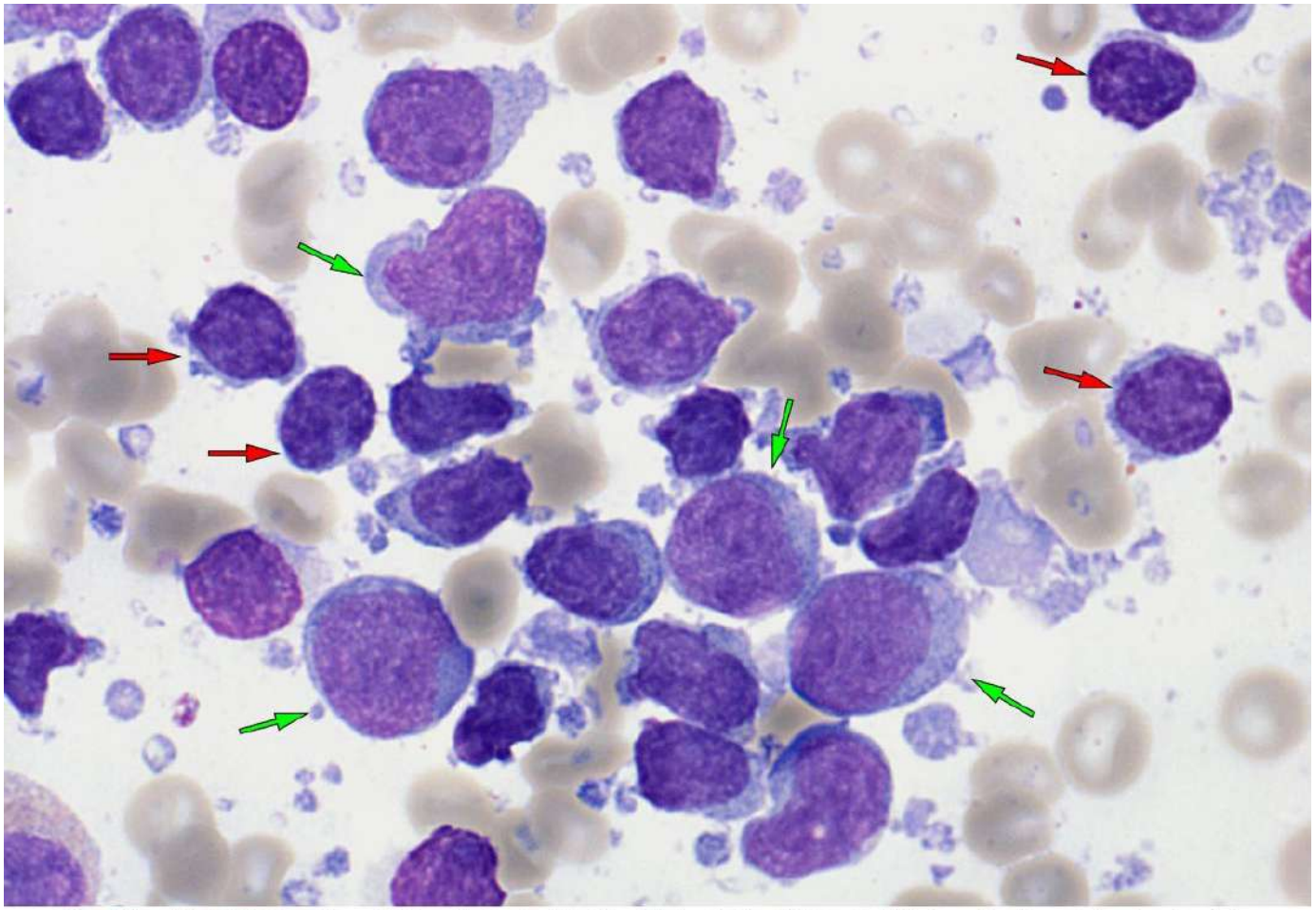
CLL/SLL.; Peripheral blood film showing small lymphocytes and smudge or smear cells (arrows).

Richter Transformation

Immunoblastic, large- cell transformation (Richter's syndrome) is the **most common form of transformation** in CLL.

The change occurs usually in one or several lymph nodes which show the features of diffuse large B - cell lymphoma (DLBCL).





Atlas of Hematological Cytology. Masaryk University, Faculty of Medicine / University Hospital Brno. Available from: http://www.leukemia-cell.org/atlas

Some of the cells are small lymphocytes with dark clumped chromatin, with scanty cytoplasm and regular outlines (red arrows). Other cells with an appearance of blasts (green arrows), large cells have less mature (open) chromatin, a high nuclear-cytoplasmic ratio and mostly one prominent nucleolus.

2- Follicular Lymphoma

- Low to intermediate grade lymphoma.

- Patients are elderly with generalized lymphadenopathy with a median age of onset of 60 years..

Gross; shows neoplastic nodules bulge onto the cut surface.

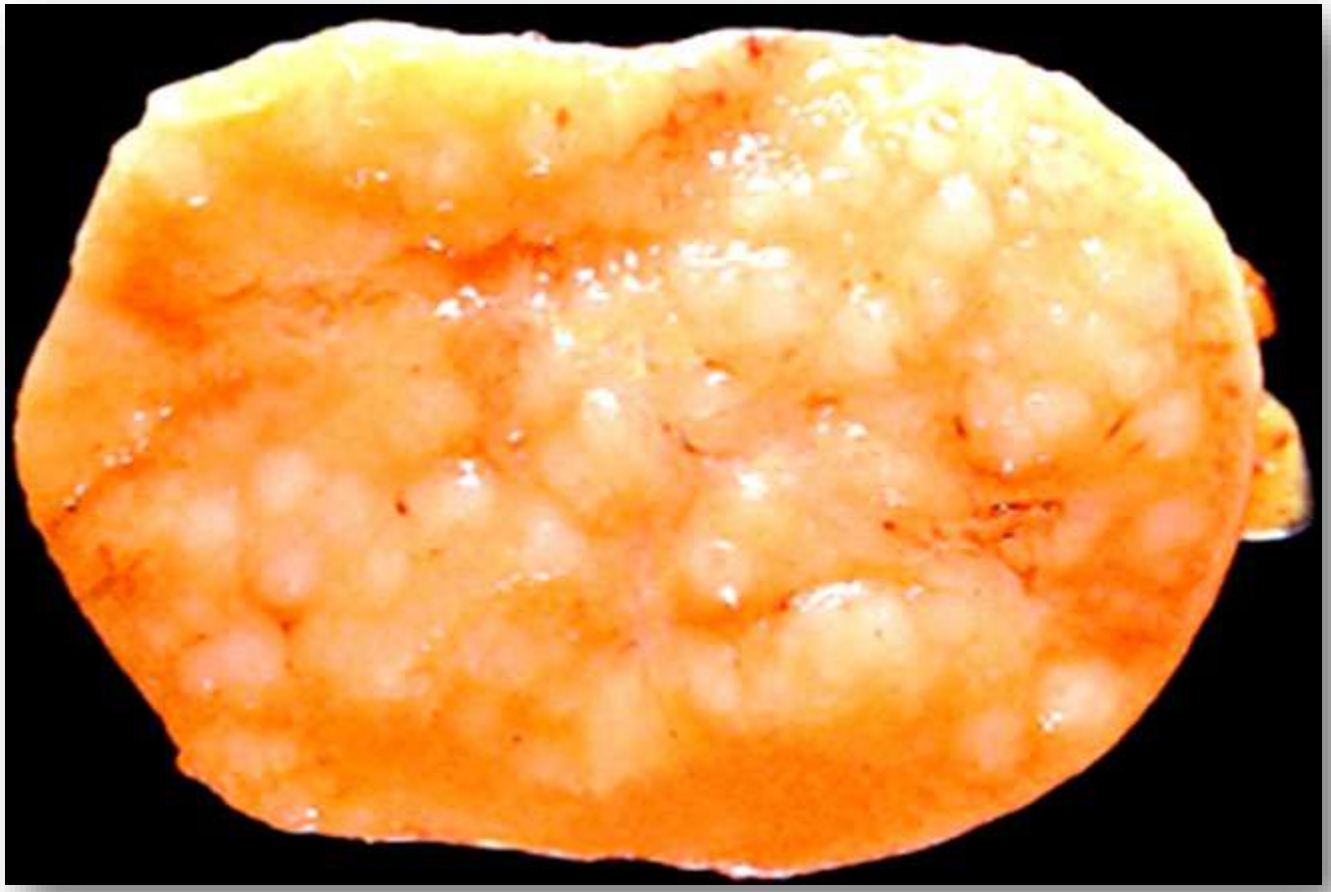
Microscopically; two types of cells are seen:

1-Centrocytes: are small lymphoid cells with irregular nuclear contours and indentations (cleaved).

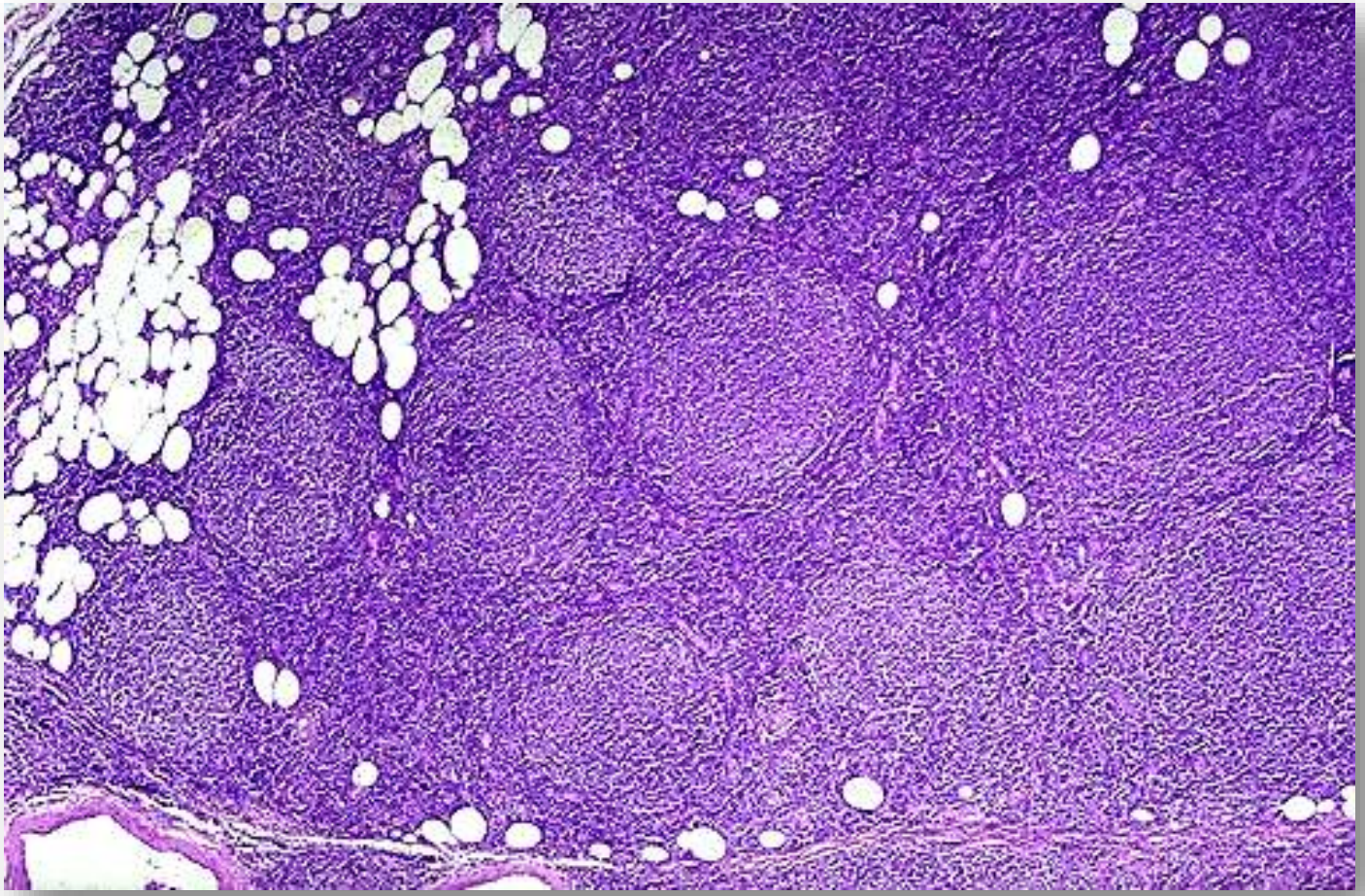
2-Centroblasts: are large cells with open chromatin and multiple nucleoli adjacent to the nuclear membrane.

- Bone marrow is involved in 70% of the cases.

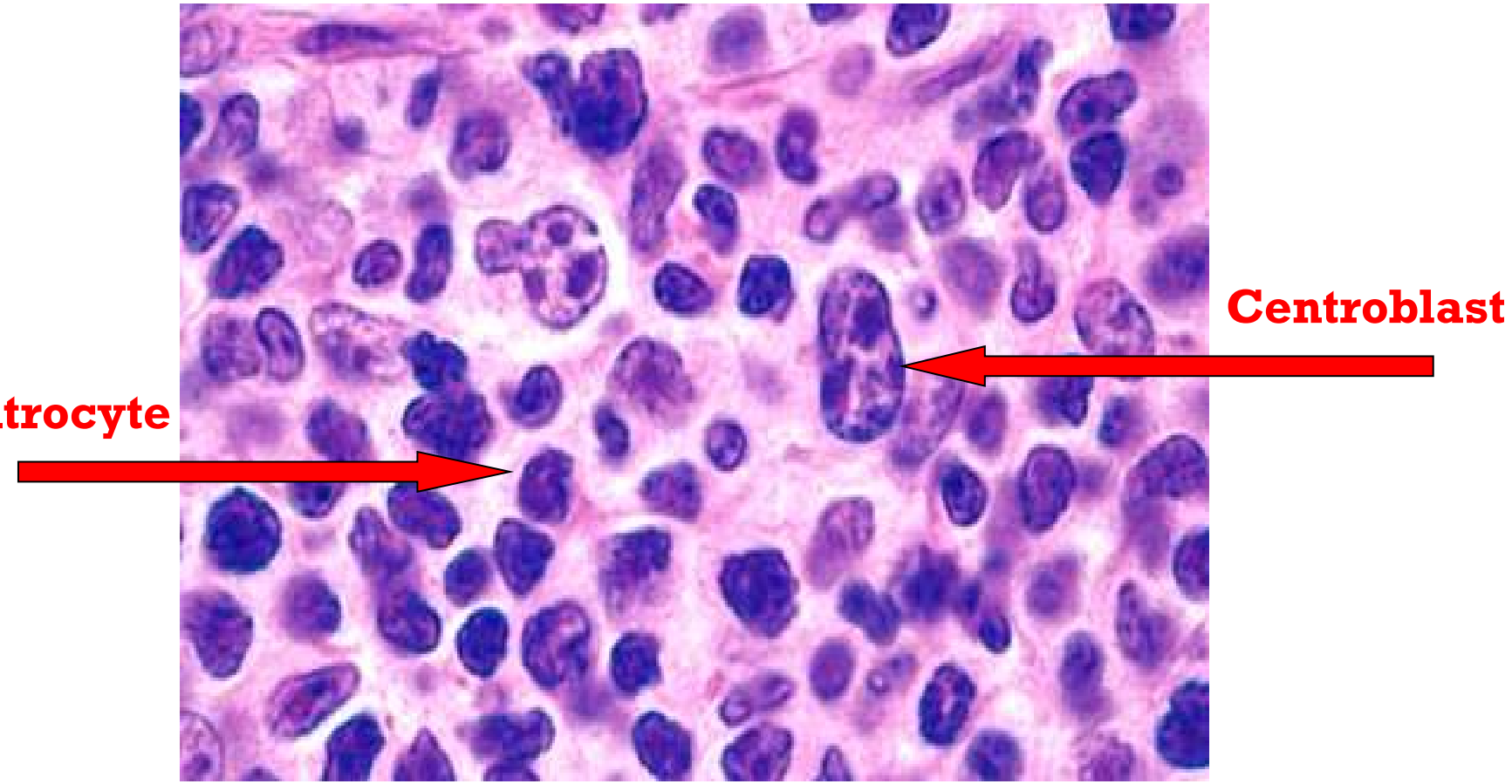
- 85% of the cases have ***t(14;18)***.



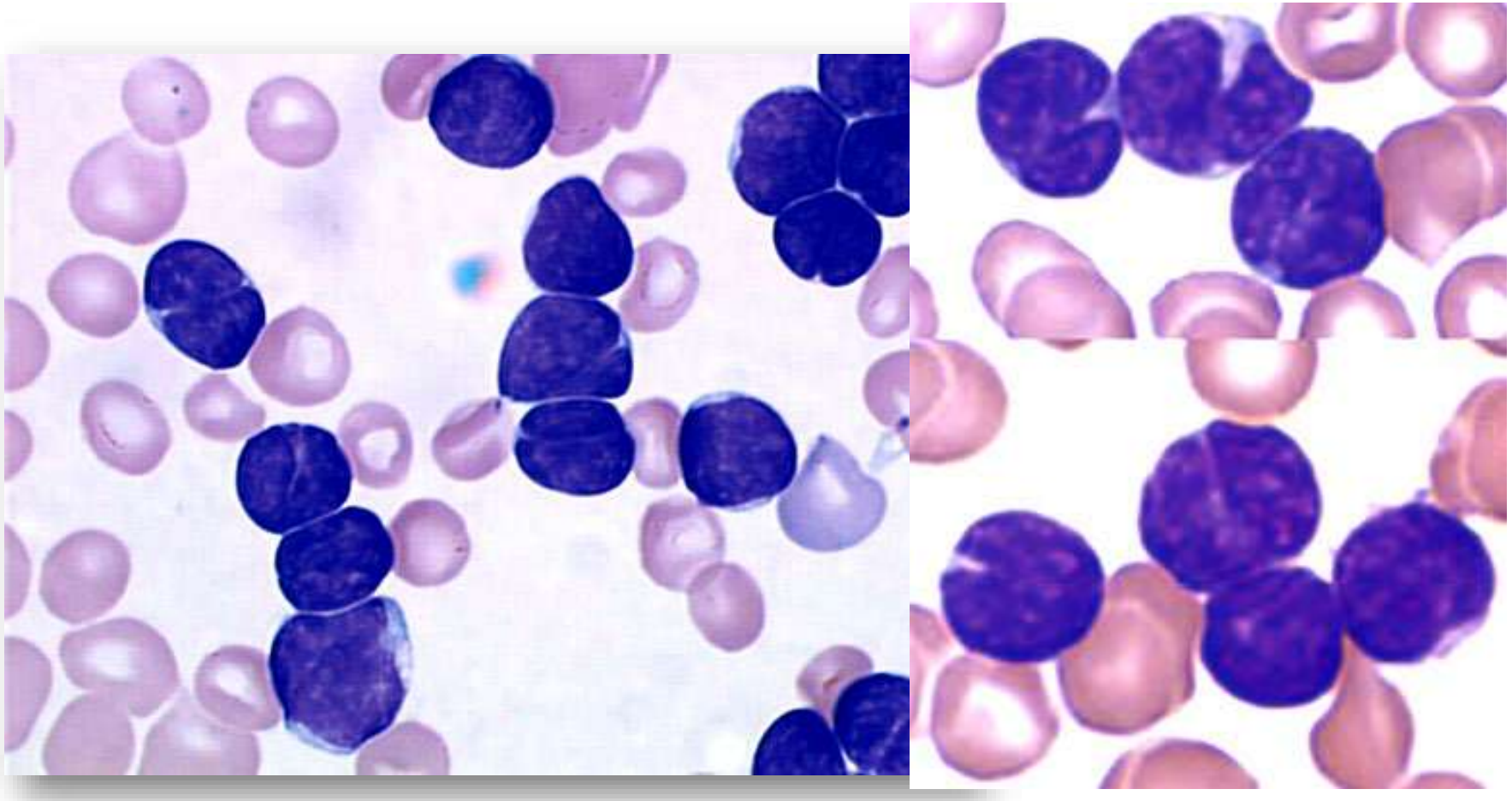
Follicular Lymphoma; LN, shows neoplastic nodules bulge onto the cut surface.



Follicular lymphoma; LN shows numerous follicles of irregular sizes.



High magnification, small lymphoid cells with condensed chromatin and irregular or cleaved nuclear outlines (centrocytes) are mixed with a population of larger cells with nucleoli (centroblasts).



Blood film of follicular lymphoma; The cells show cleaved nucleus (irregular outline) with low N/C ratio.


thank you
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