Diseases of Lymphatic System

Sites of Lymphoid Tissue

- The lymphoid tissue exists in: bone marrow (B.M.), thymus, lymph nodes (L.Ns.), spleen, lymphoid tissue in the nasopharynx, tonsils, Peyer's patches of the terminal ileum, appendix and bronchus associated lymphoid tissue.
- The lymphoid tissue exists also in: yolk sac, fetal liver of the embryo.

- Bone marrow, yolk sac, fetal liver and thymus are known as **“Primary lymphoid organs”**.
- **“Secondary lymphoid organs”** include lymph nodes, spleen, tonsils, Payer's patches and appendix.

- These organs and tissues have traditionally been divided into **myeloid tissue**, which includes the bone marrow and the cells derived from it (erythrocytes, platelets, granulocytes and monocytes), and **lymphoid tissue**, consisting of thymus, (L.Ns.) and spleen.

Normal anatomy of L.Ns.

- The three major regions of a L.Ns. are the cortex, paracortex, and medulla.
- **The cortex:**
- It is situated beneath the capsule and contains the lymphoid follicles which are formed of the following three zones from inside outwards:

1. **Pale germinal center:** formed of:

- Follicle center cells (B lymphocytes) of two types; small centrocytes with cleaved nuclei.
- Macrophages; engulf cell debris in case of hyperplasia.

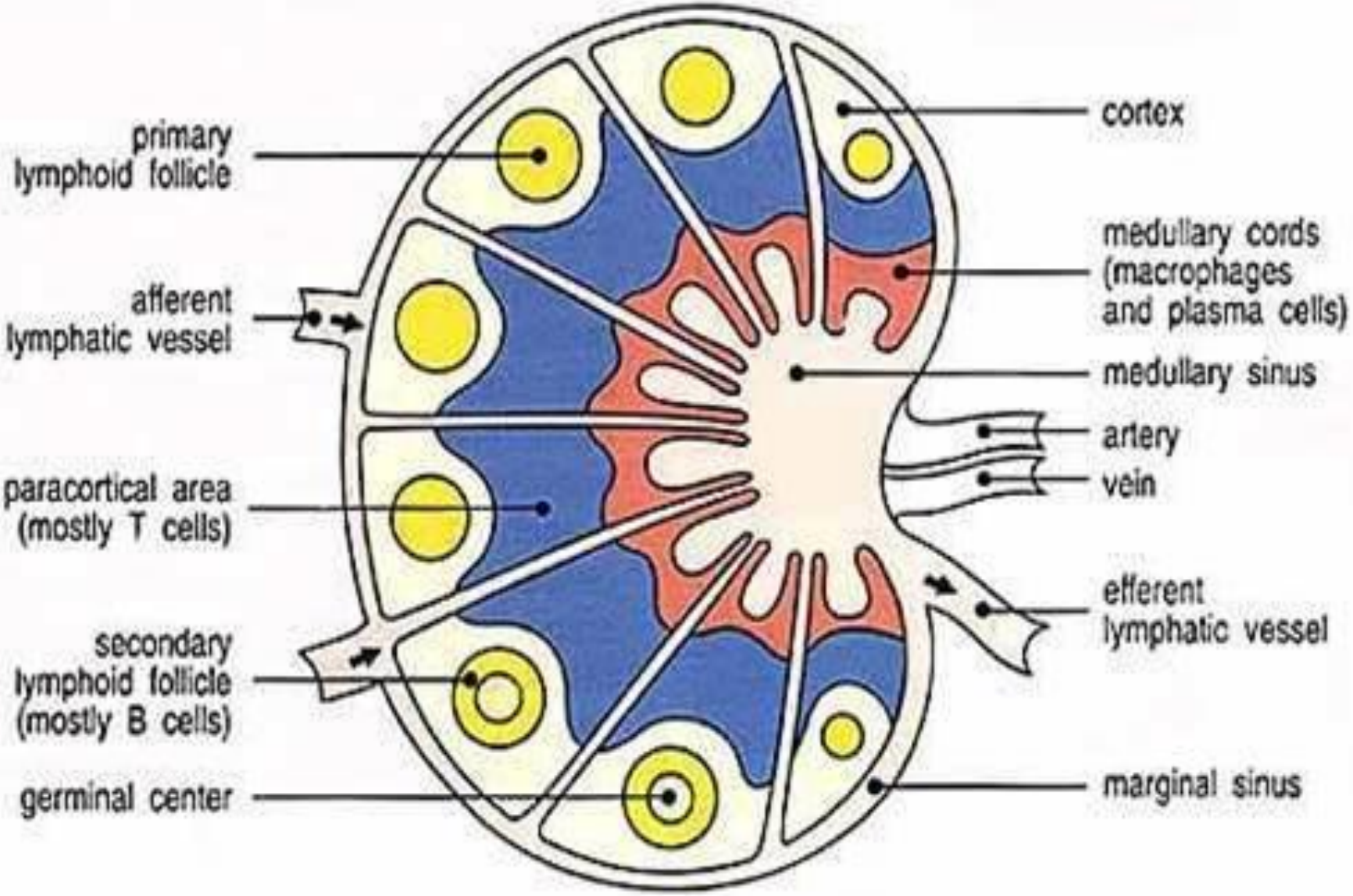
2. **Mantle zone:** tightly packed small B lymphocytes.
3. **Marginal zone**: less tightly packed mature B lymphocytes present in hyperplasic lymphoid follicles.

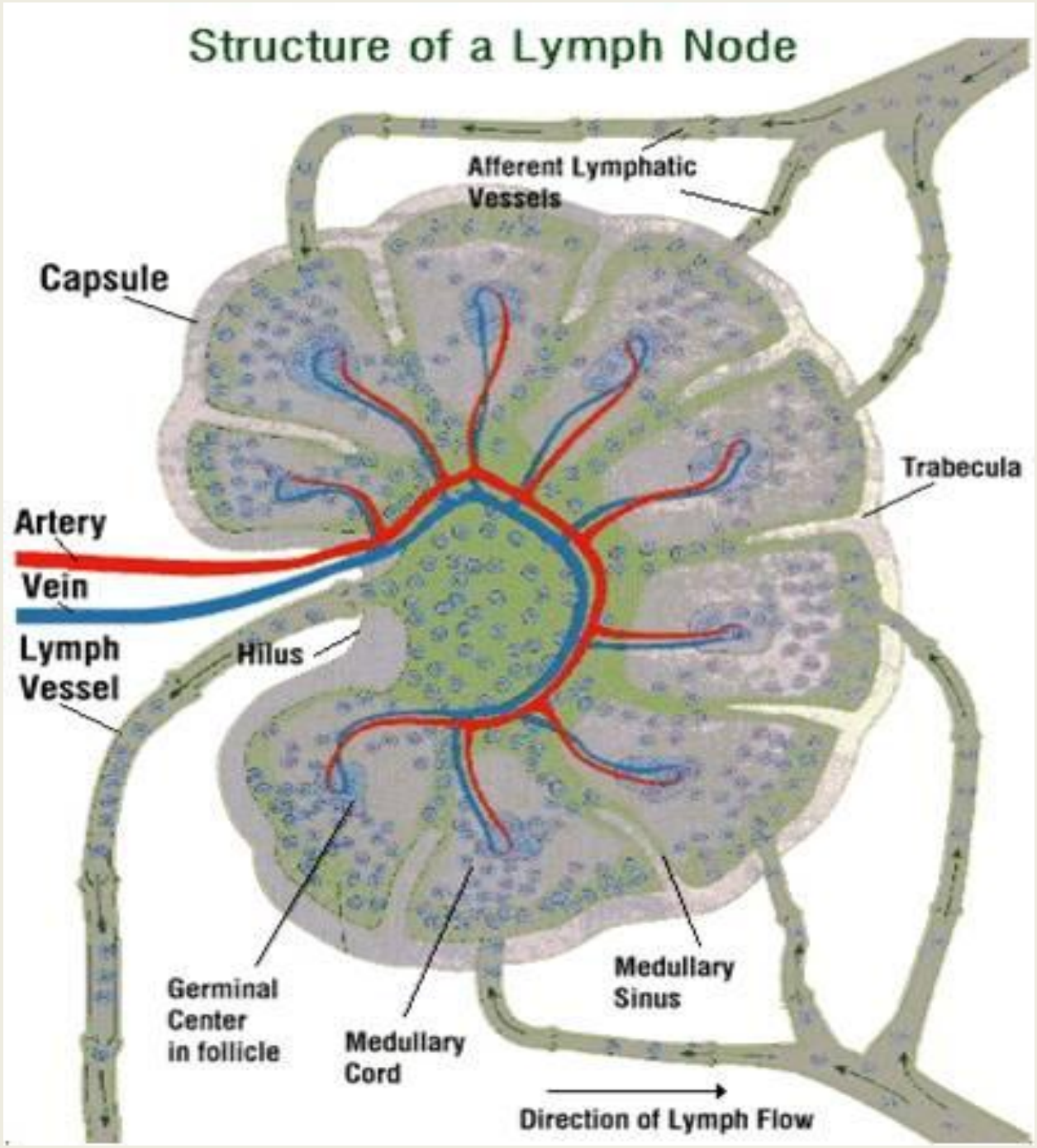
- **The paracortex**: it is the zone situated between the cortex and medulla, which contains T lymphocytes, reticulum cells and immunoblasts (activated B or T lymphocytes) which have abundant eosinophilic cytoplasm and large vesicular nuclei with prominent eosinophilic nucleoli.

- **The medulla:**
- It is close to the hilum and it is rich in lymphatic sinuses, arteries and veins.
- It is only a minor lymphocytic component formed of mature B lymphocytes, plasmocytoid lymphocytes, plasma cells migrating from the cortex and responible for humoral immunity.

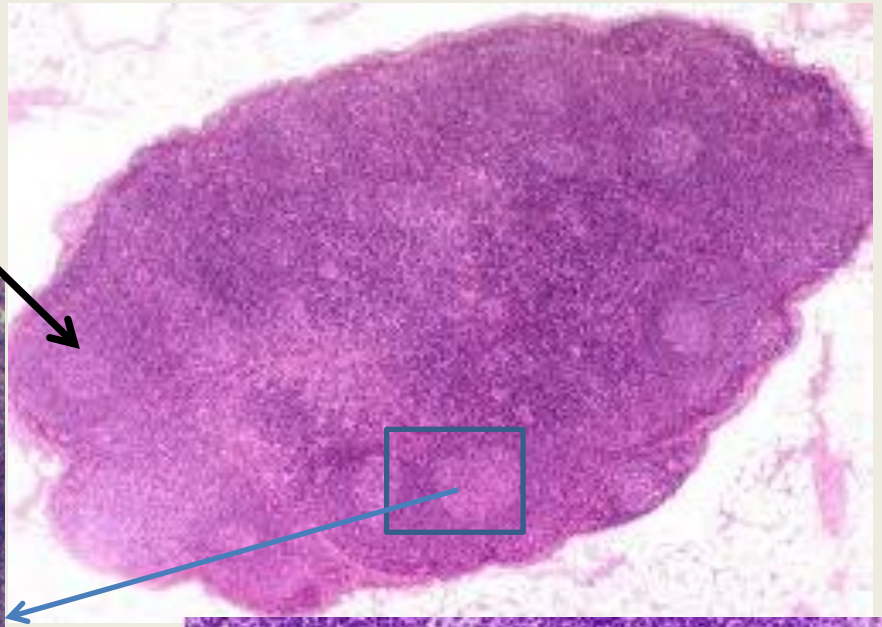
- Under normal condition lymph nodes are small, bean shaped structure which, even in their more peripheral locations (e.g. cervical, axillary and inguinal) are seldom palpable.
- The capsule is perforated by multiple afferent lymphatics that empty into a fenestrated subcapsular peripheral sinus.

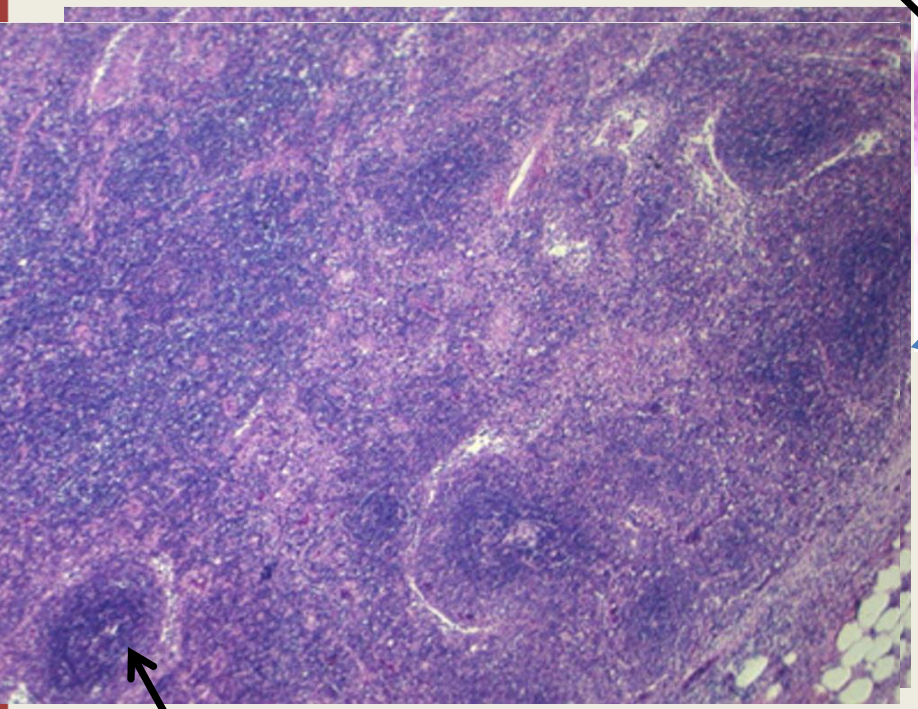
The lymph node



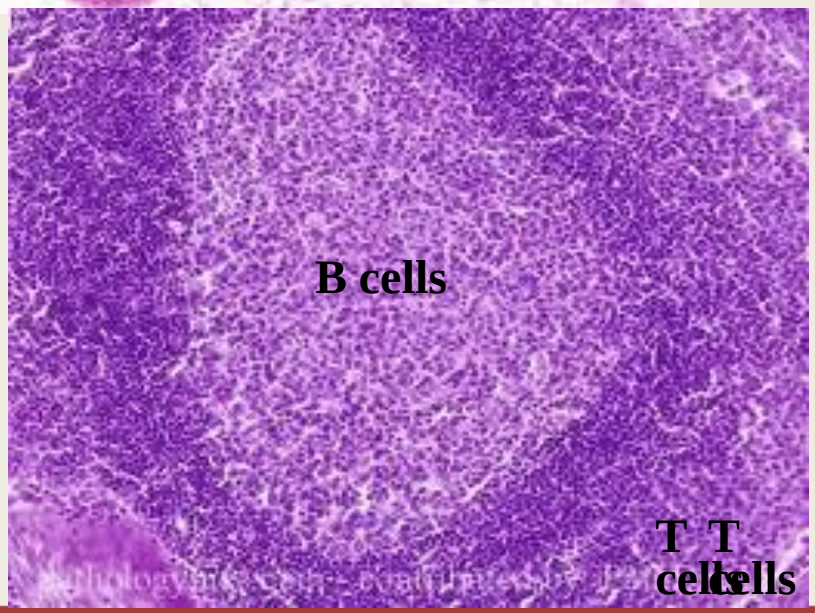

Structure of a Lymph Node
Afferent Lymphatic Vessels
Capsule
Trabecula
Artery
Vein
Lymph Vessel
Hilus
Germinal Center in follicle
Medullary Cord
Medullary Sinus
Direction of Lymph Flow

Secondary follicle





Primary follicle



Inflammatory and hyperplastic diseases

1. **Acute non specific lymphadenitis:**

- It usually occurs in L.Ns. draining acutely inflamed focus e.g. acute suppurative tonsillitis or abscess.
- It leads to nodal acute inflammatory reaction, rich in neutrophils.
- **Morphology:** The L.Ns. are enlarged and may be the seat of abscess formation.

2. **Chronic non specific lymphadenitis:**

- The condition assume one of three patterns depending on the causative agent:

a. **Reactive follicular hyperplasia:**

- The lymphoid follicles are prominent with enlargement of their germinal centers. It is associated with inflammatory processes that activate B cells as rheumatoid arthritis, toxoplasmosis, and HIV.

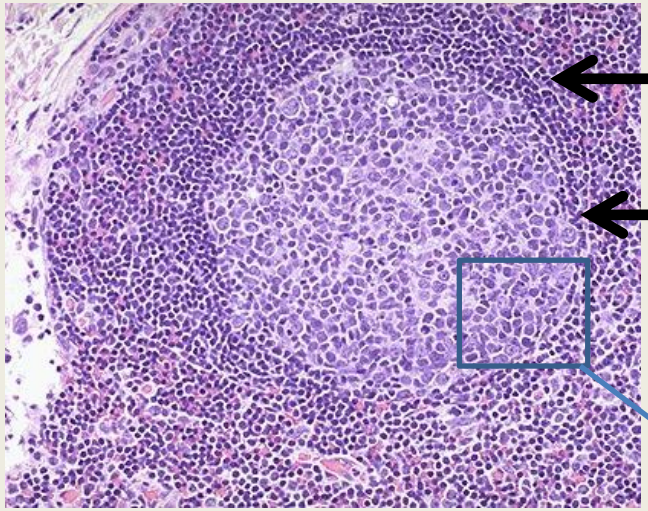
b. **Paracortical hyperplasia:**

- It is due to activation of the parafollicular T cells as in viral infection (EBV), follows vaccination, or application of certain drugs as phenytoin.

c. **Sinus histiocytosis:**

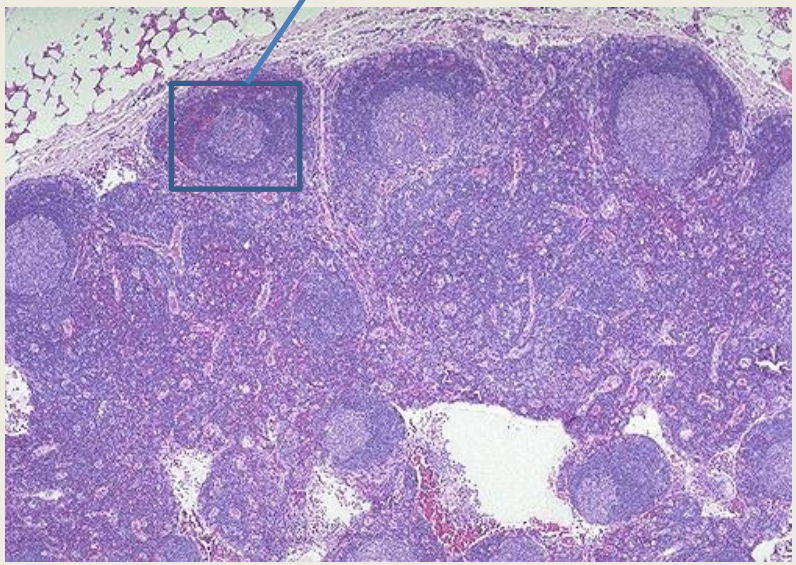
- The medullary sinuses are loaded with histiocytes. It is often encountered in nodes draining cancer (represent immune reaction to the tumor or its products).

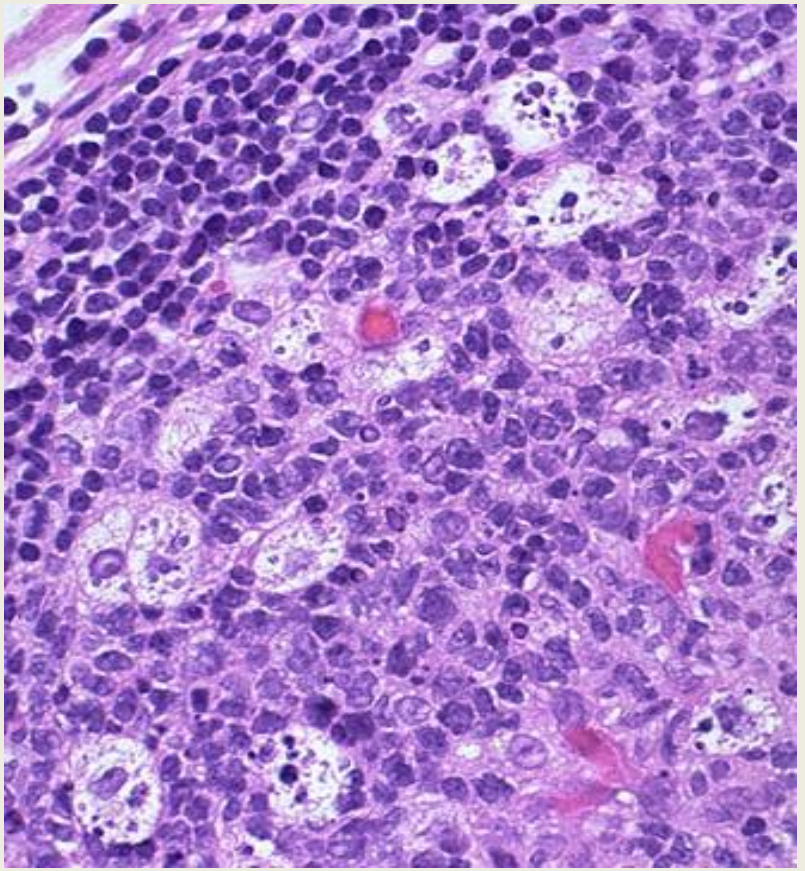
REACTIVE HYPERPLASIA



Mantle zone

Secondary follicle



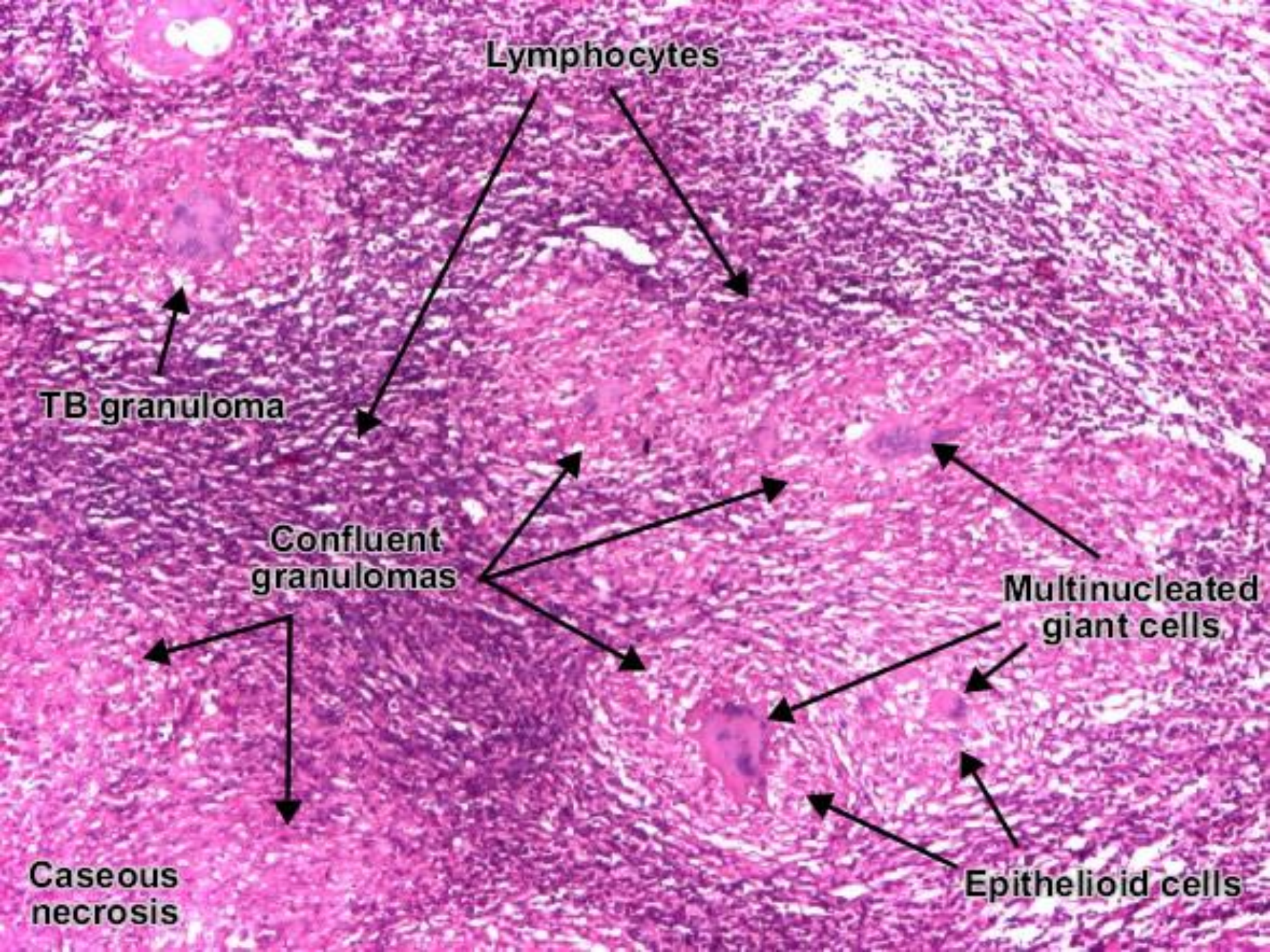


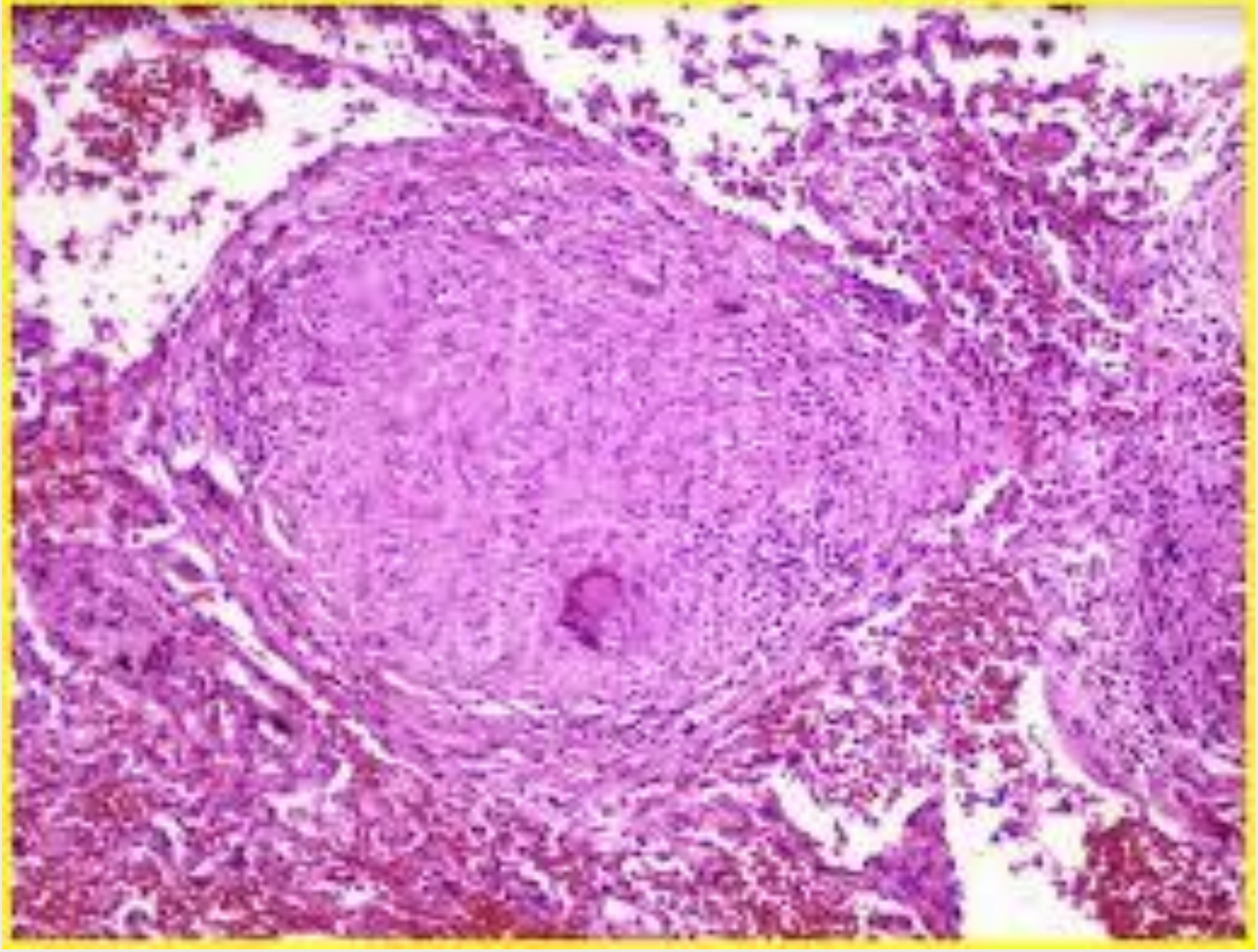
3. **Chronic specific lymphadenitis; Granulomatous lymphadenitis:**

a. **Tuberculosis:**

- **Gross picture:**
- **Early:** The L.Ns. are enlarged firm and not adherent together with grayish white cut surface.
- **Late lesions:** The L.Ns. become adherent to each other (matted together) due to periadinitis.
- The cut surface show cheesy-like yellowish material (caseous necrosis).

- **Microscopic picture:**
- **Early tuberculous lymphadenitis:** There is multiple infiltration by multiple small pale tubercle formed of aggregates of epithelioid cells, few Langhan's giant cells and minimal caseation.
- **Caseating tuberculous lymphadenitis:** Most of nodal tissue is replaced by areas of caseous necrosis with multiple small tubercles at the periphery.


Lymphocytes
TB granuloma
Confluent granulomas
Multinucleated giant cells
Caseous necrosis
Epithelioid cells



- **Complications and effects:**
- TB cervical lymphadenitis: Cold abscess with multiple sinuses discharging caseous material. TB of the skin around these sinuses.
- TB medistinal lymphadenitis: Pressure manifestation (mediastinal syndrome). Spread of infection to the lung.
- TB mesentric lymphadenitis: Rupture of caseous L.Ns. Leading to TB peritonitis.
- In addition to the following complications:
  - Pathological calcification.
  - Hematogenous dissemination.
  - Secondary amyloidosis.

b. Sarcoidosis: It is a disease forming non caseating epithelioid cell granuloma. The disease usually begins in the lungs, skin, or lymph nodes

c. Toxoplasmosis: The disease presented by muscle aches and tender. It is caused by toxoplasma gonadii. It forms non caseating epithelioid cell mirogranuloma. Toxoplasmin test is a diagnostic serological test.

d. Crohn's disease: One of the inflammatory bowel disease of the intestine that forms non caseating epithelioid cell granuloma in the GIT wall.

e. Cat scratch disease:

- It is transmitted to man through skin scratches or bites of cats or rabbits. Axillary group of L.Ns. are usually affected.
- **Microscopic picture:** it is characterized by nodal formation of microabscesses having central stellate shaped areas of necrosis with neutrophiles surrounded by palisading of histiocytes i.e., stellate necrotizing granuloma.

4. Infectious mononucleosis:

- It is a rare viral disease causing generalized lymphadenopathy, splenomegaly, mild fever, and sore throat.
- **Microscopic picture:** There is partial loss of nodal architecture with marked diffuse paracortical proliferation of atypical B cell forms. This picture may be confused with malignant lymphoma.

- **Diagnosis:**

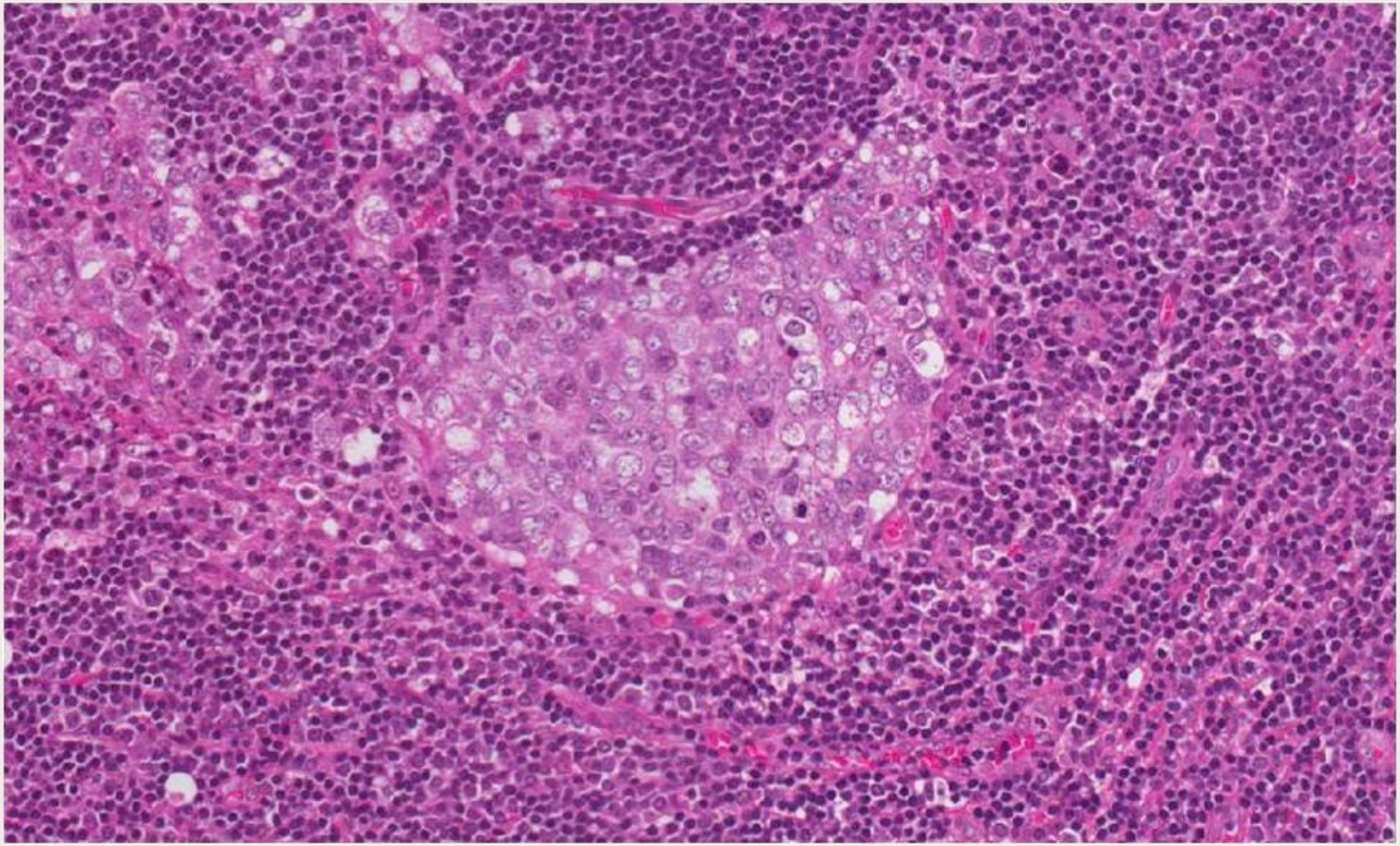
1. Lymphocytosis with atypical lymphocytes in peripheral blood.
2. Positive hetrophil reaction (monospot test).
3. A rising titer of specific EBV antibodies.

Tumors of lymphoid tissue

- Tumors of L.Ns. are either primary or secondary.
- **Primary tumors:**
- All are malignant and are called lymphomas.
- They arise from nodal or extranodal lymphoid tissue.

- **Secondary tumors:** These are the metastatic tumors which occur in L.Ns. draining primary site of malignancy.
- They are more frequent than the primary group and occurs in L.Ns. draining carcinoma.
- The L.Ns. are enlarged firm fixed.
- The cut surface is grayish white.

Metastatic Carcinoma of the L.N.



Lymphoma

- They are primary malignant tumors of the lymphoid tissue.
- They include tumors arising from T or B lymphocytes, histiocytes, monocytes, or reticulum cell. The most common type is that of lymphocytic origin, particularly B type.

- **Lymphoma can be divided into two main categories:**

  A. Hodgkin's Lymphoma (HL).

  B. Non-Hodgkin's Lymphoma (NHL).

Hodgkin's Lymphoma

- It is tumor of B lymphocytes.
- **Incidence**
- Common disease representing ~30% of all lymphomas.
- Biphasic age incidence.

- **Clinical picture:**
- The disease occurs mainly in young and middle aged persons with peak at the third decade and a male predominance. The disease may presented by:

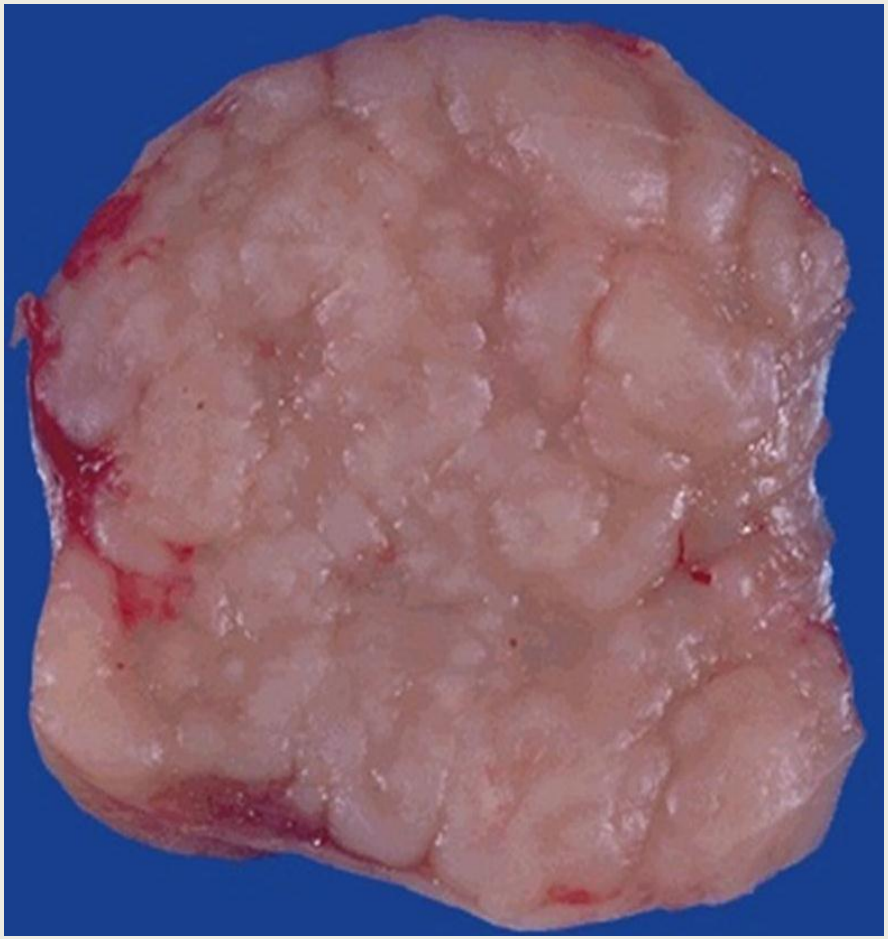
1. Painless non tender enlarged L.N.
2. Mild intermittent fever, lasting for few days and followed by normal temperature for one or two weeks. This is called Pel-Epstein fever.

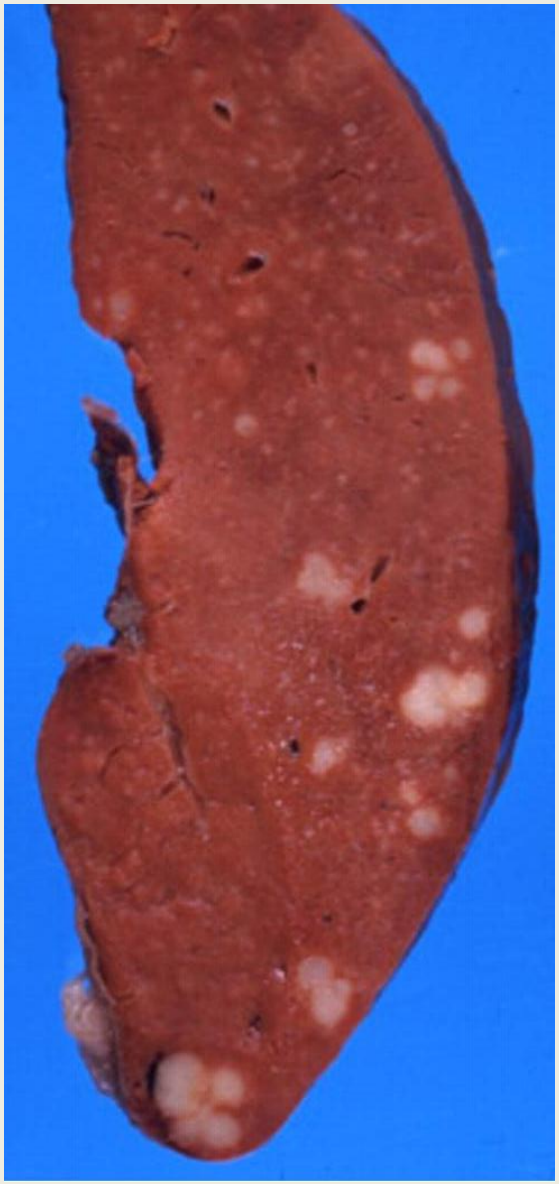
3. Progressive anemia.
4. Loss of weight.
5. Itching.
6. Pressure manifestations caused by the enlarged L.Ns.

- **Gross picture:** L.Ns. Are enlarged, firm, rubbery, discrete, but may become adherent later on due to invasion of the capsule.
- The cut surface is homogenous greyish pink in color.

Hodgkin`s Lymphoma

Gross picture:

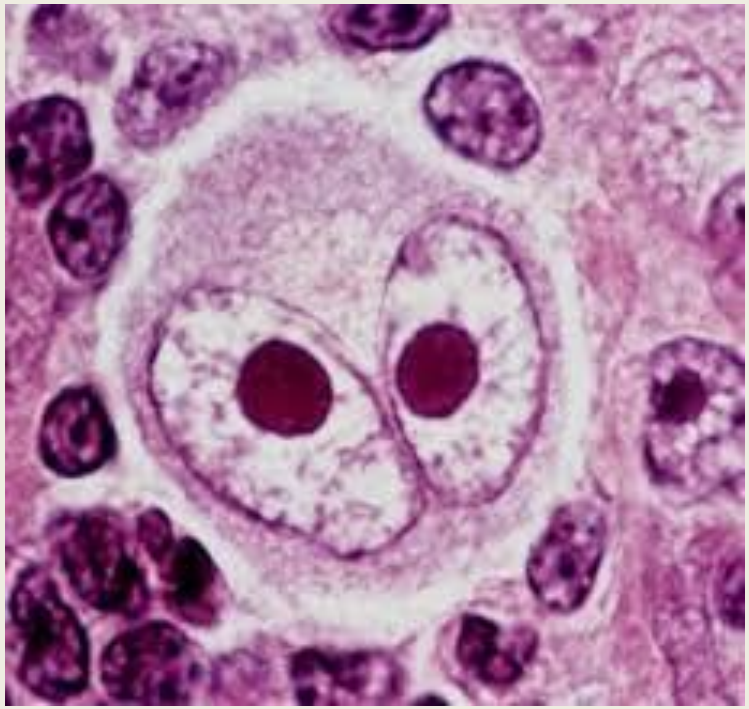


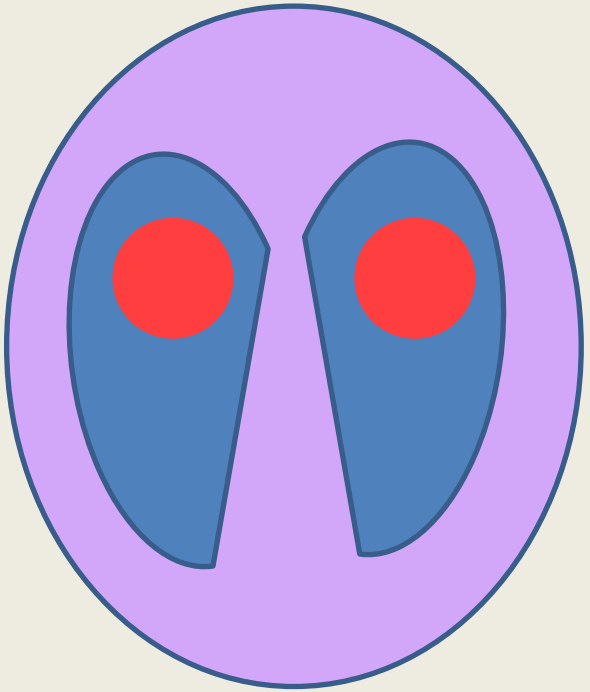


- **Microscopic picture:** It is characterized by the presence of malignant giant cells termed **“Reed-Sternberg cells”** in a background of non-neoplastic small lymphocytes and a heterogeneous population of benign inflammatory cells.

- **Reed-Sternberg cells (RSCs):**
- The classic RSC; is a large cell with an abundant weakly eosinophilic cytoplasm. The nucleus is bilobed or polylobed with prominent nucleoli.
- In the most typical form; the diagnostic RSC show two nuclei or nuclear lobes facing each other **(mirror image)**. Each lobe contains a large acidophilic nucleolus surrounded by clear zone giving an **"Owl eye"** appearance.

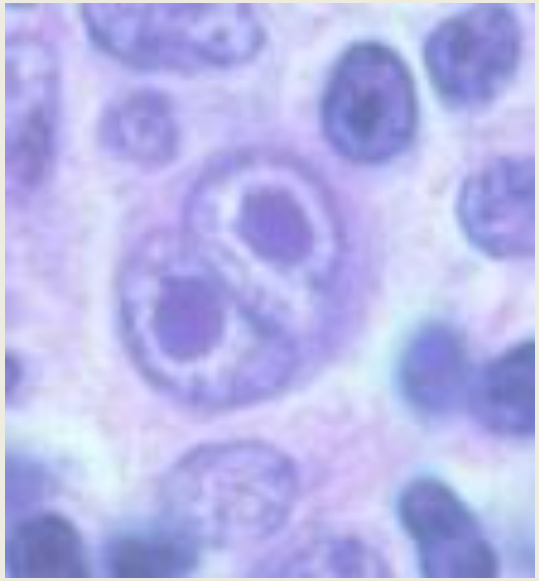
Reed-Sternberg cells (RSCs)

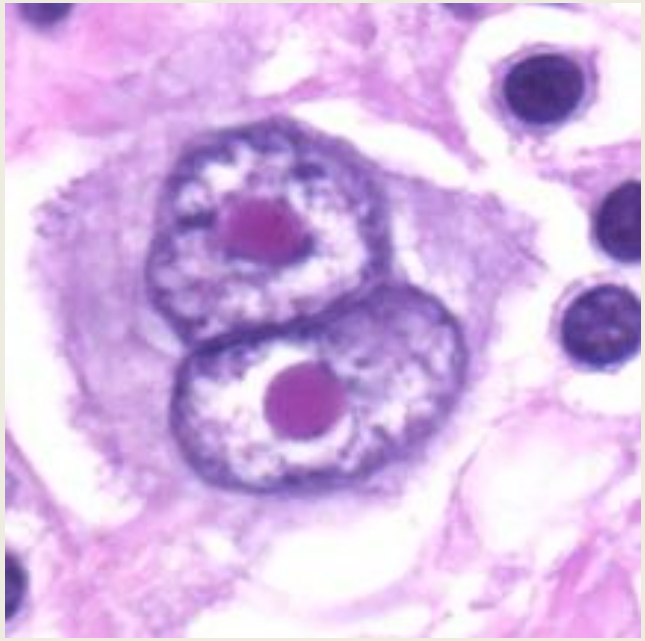


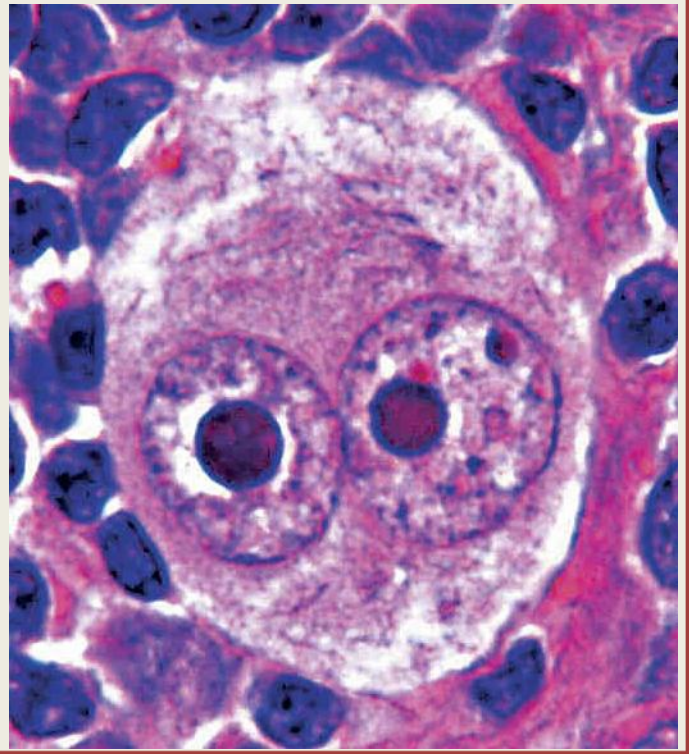


Reed-Sternberg cells (RSCs)

Microscopic picture:





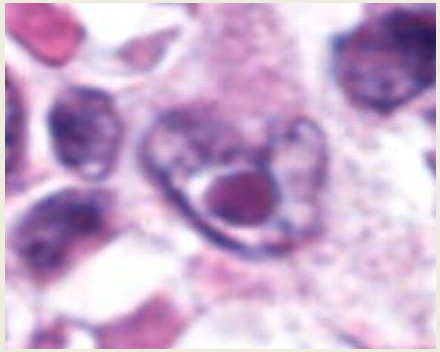


- **Atypical variants of RSCs include:**
- **Lymphocytic-histiocytic (L&H); Popcorn variant:** The nucleus is puffy, multilobed with small punctuate nucleoli and scanty cytoplasm.
- **Lacunar variant:** The nucleus is single to multilobed. The nucleolus is relatively small. The cytoplasm may retract or shrunken and the cell appears to lie in a clear space or lacuna (clear space between shrunken cytoplasm and cell wall).

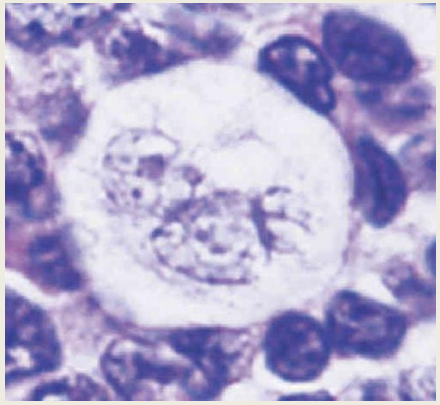
- **Pleomorphic variant:** The nucleus is single, irregular or multilobed. The nucleoli are variable in size.
- **Mononuclear variant:** This large cell contains one nucleus with large eosinophilic nucleolus.
- **Immunohistochemistry:** The classic RSC and its variants are positively stained by CD15 and CD30 antibodies which are diagnostic.

Variants of Reed-Sternberg cells:

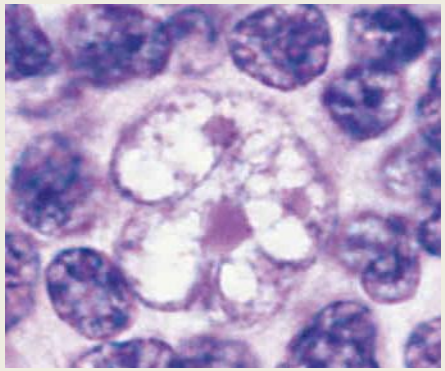
Mononuclear variant



Lacunar cell



Lymphocytic & Histiocytic (L&H) Popcorn variant



Classification of Hodgkin's Lymphoma

- **Microscopic subtypes:**
- According to the frequency and type of RSCs, predominant background cell type, and occurrence of fibrosis, H.L. is classified into:

Hodgkin`s Lymphoma

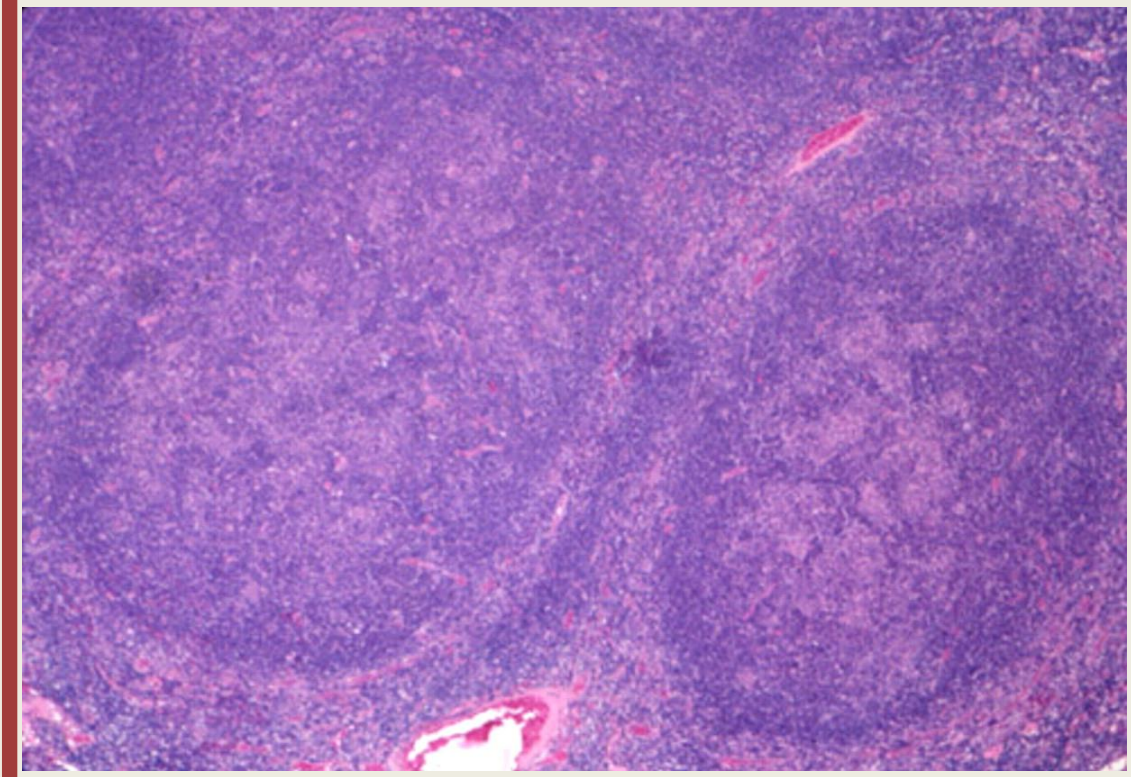
Classification:

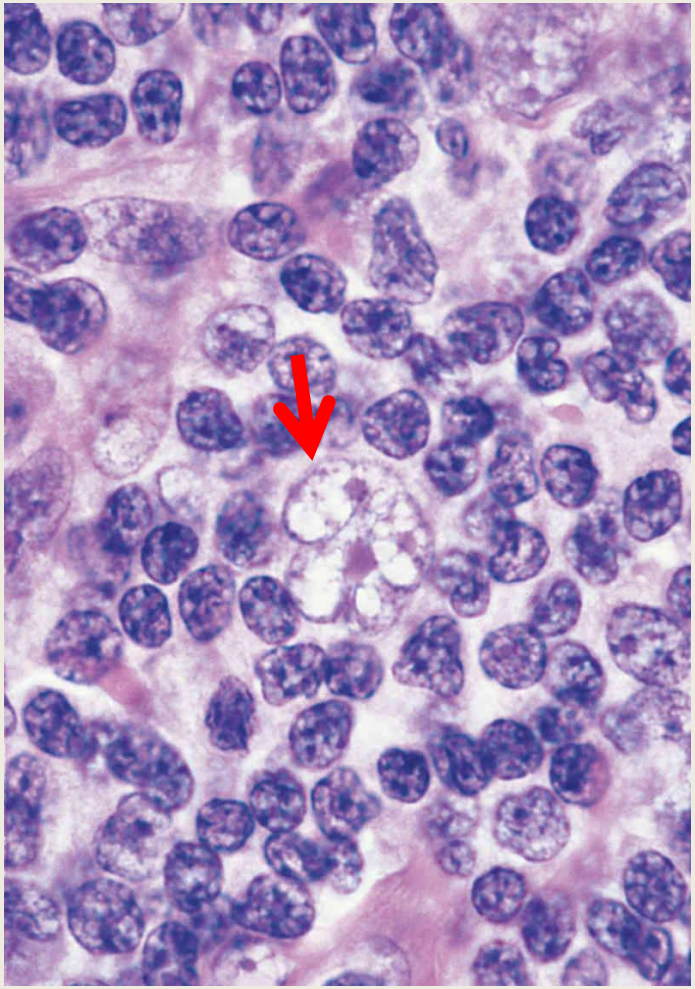
- **Classical HL (95%)**
  - **Lymphocyte predominant classical HL (5%)**
  - **Nodular sclerosis HL (65%)**
  - **Mixed cellularity HL (20-25%)**
  - **Lymphocyte depletion HL (<5%)**
- **Nodular lymphocyte predominant HL (5%)**

- **Nodular lymphocyte predominant HL:**
  - Represents about 5% of all HL cases
  - Has the best prognosis
  - **Characterised by:**
    - Loss of normal nodal architecture
    - Nodular infiltrate of the lymph node consists of reactive cells (predominantly lymphocytes)
    - **Lymphocytic-histiocytic (L&H); Popcorn variant .**
    - No typical RSCs.

Hodgkin`s Lymphoma

Nodular lymphocyte predominant HL

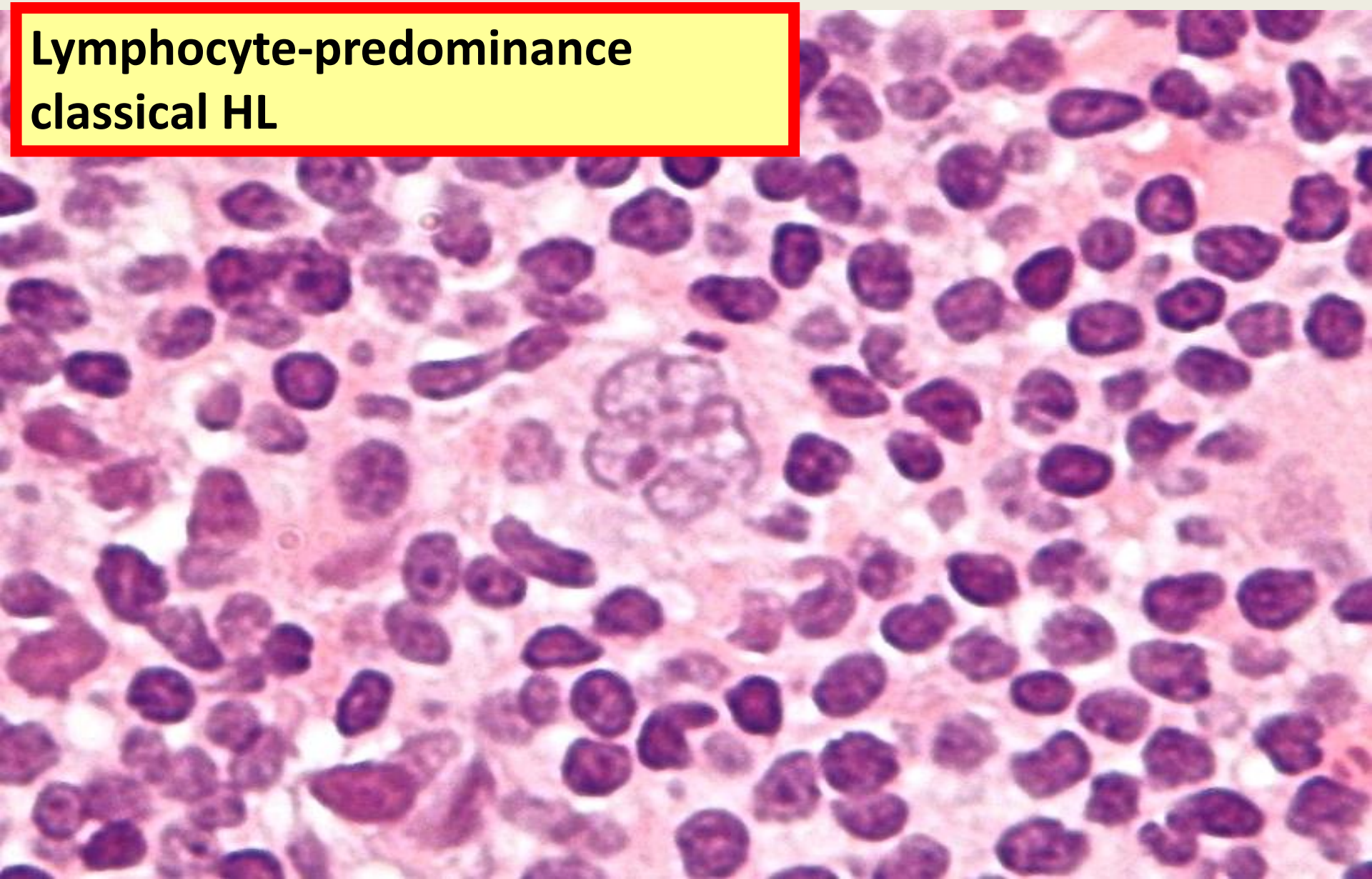




1. **Lymphocytic predominant type:**
   - The classic RSCs are rare with relative frequency of **Popcorn variant**.
   - The background is formed of mainly of small resting lymphocytes, eosinophils, plasma cells and histiocytes. in a diffuse pattern replacing the nodal architecture.
   - Has good prognosis
   - It is characterised by
     - Diffuse pattern
     - Loss of normal nodal architecture

Hodgkin`s Lymphoma

Lymphocyte-predominance classical HL

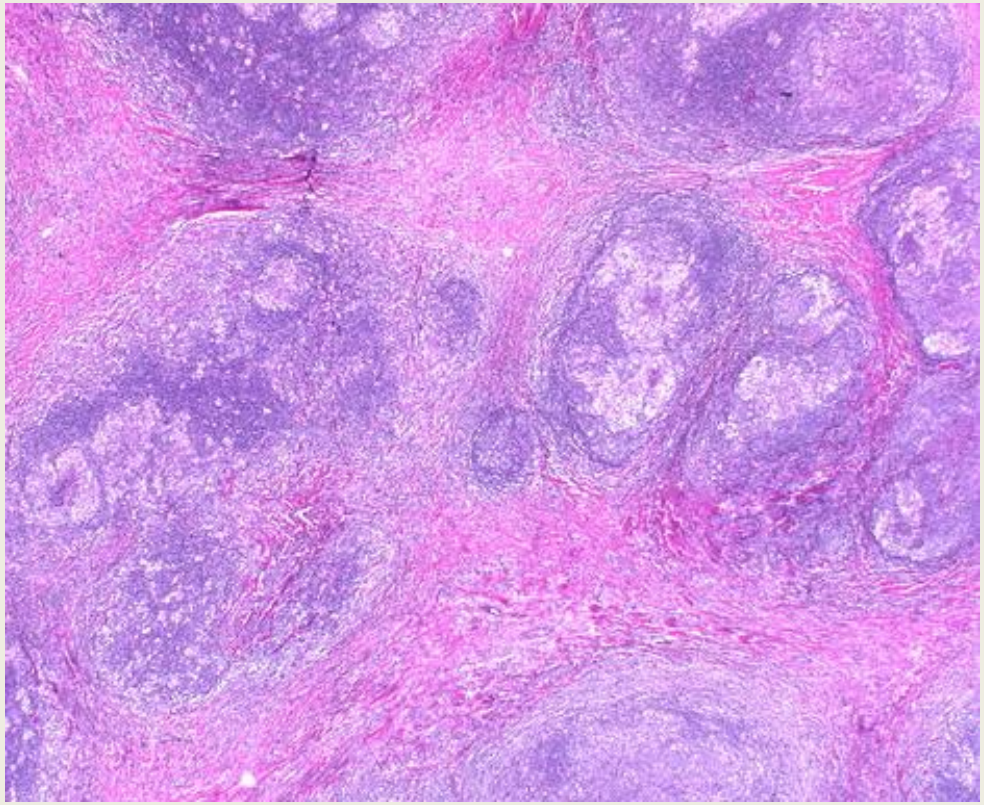


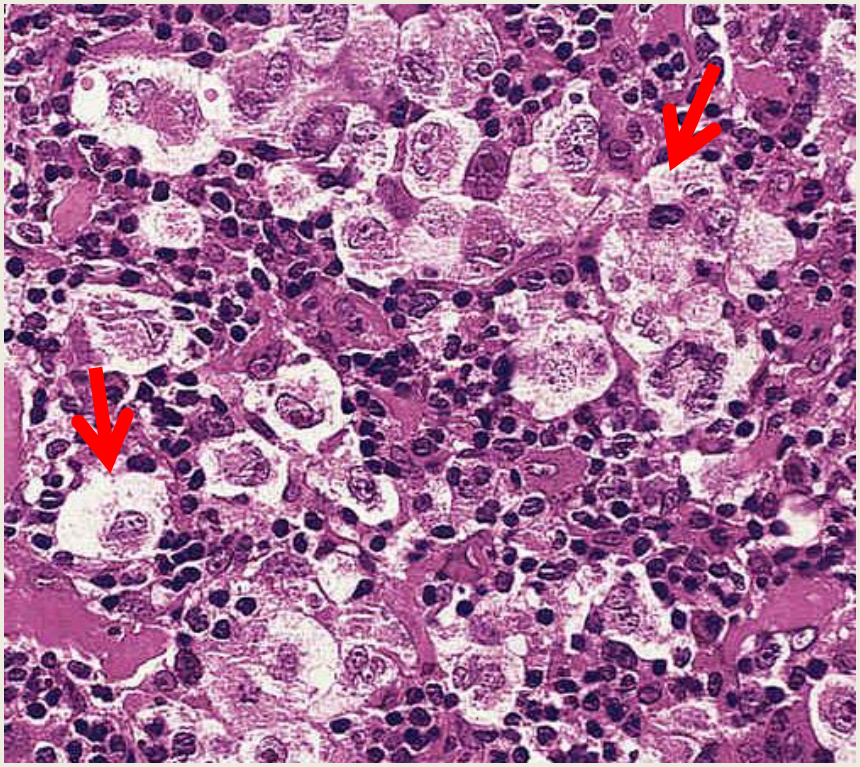
2. Nodular sclerosing type:

- The classic RSCs are very rare
- Large number of lacunar cell variant.
- The background is formed of variable amounts of small lymphocytes as well as mixed inflammatory cells.
- These are divided into nodules by dense bands of fibrous tissue.
- This type has favorable prognosis.

Hodgkin`s Lymphoma

Nodular sclerosing HL



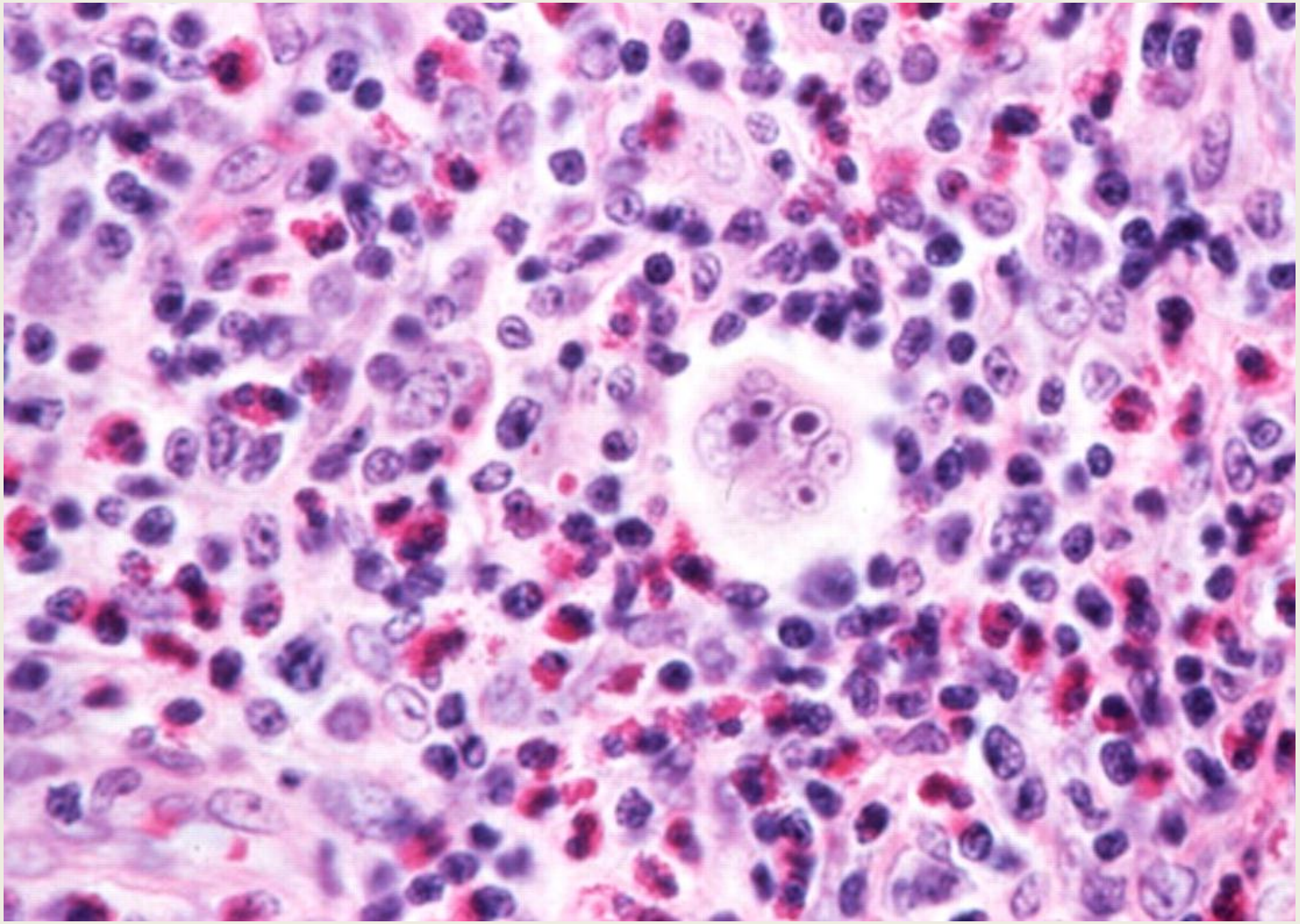


3. Mixed cellularity type:

- The classic RSCs are easily identified.
- A background is formed of diffuse mixed inflammatory cells including eosinophils, plasma cells, polymorphs, histiocytes as well as lymphocytes.
- Characterised by:
    - Loss of normal nodal architecture
    - Has poor prognosis

Hodgkin`s Lymphoma

Mixed cellularity HL



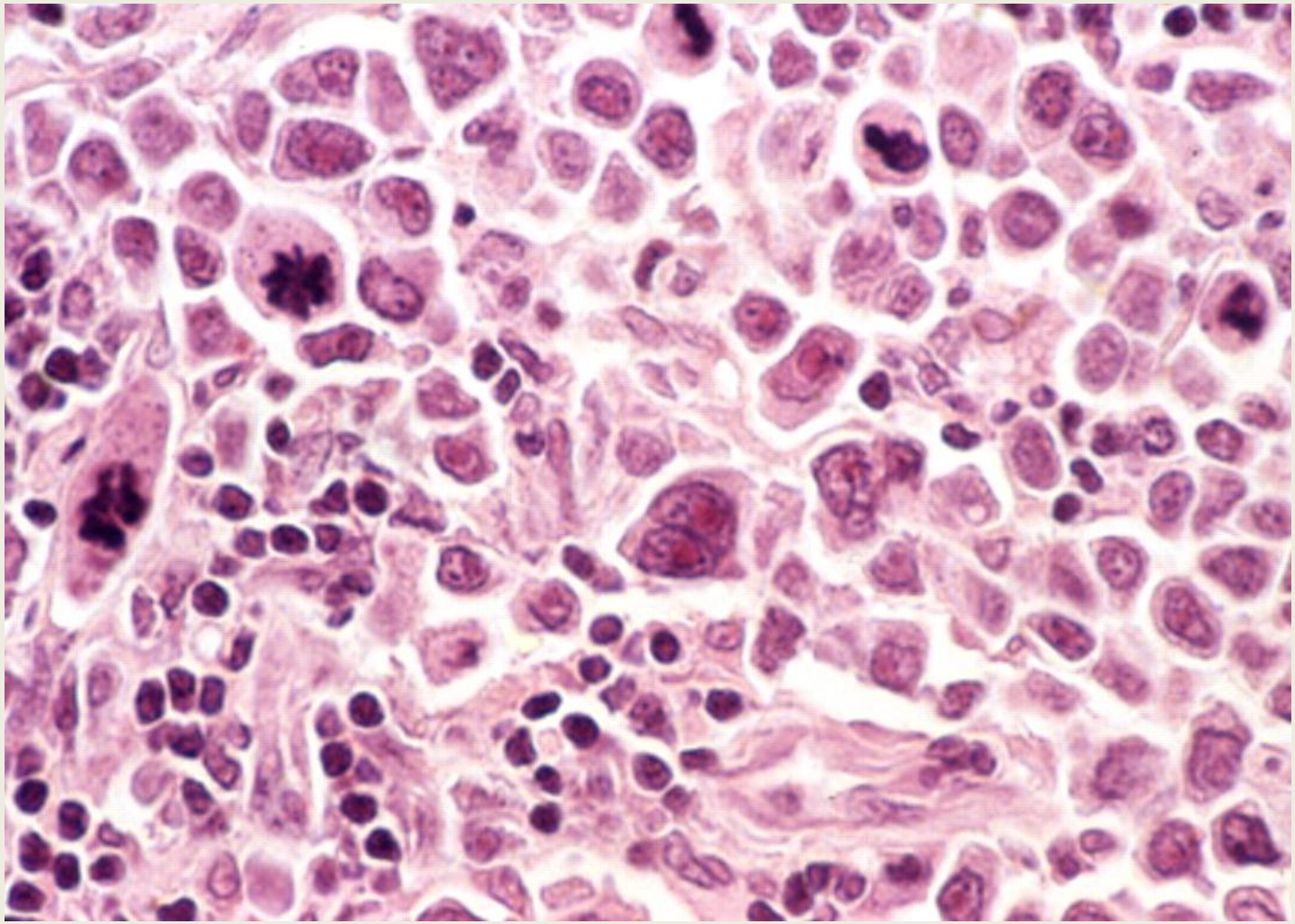
4. **Lymphocytic depletion type:**

   The classic RSCs are rare with occurrence of pleomorphic variant with frequent mitosis.

- The background is formed of few small lymphocytes as well as few mixed inflammatory cells.
- The infiltrate is diffuse and there is variable amount of fibrosis.
- This forms of fibrosis may be predominant giving rise to subtype of the disease called **lymphocytic depletion with diffuse fibrosis.**
- Has the worst prognosis.

Hodgkin`s Lymphoma

Lymphocyte depletion HL



- **Prognosis:**

- Based on histological types:
  - Nodular lymphocyte predominant and Lymphocyte rich Classical HL have good prognosis
  - Nodular sclerosis HL has relatively good prognosis
  - Mixed cellularity HL has poor prognosis
  - Lymphocyte depletion HL has worse prognosis
- Clinical stage and presence of systemic infiltration are more important than histological features in determining prognosis of HL.

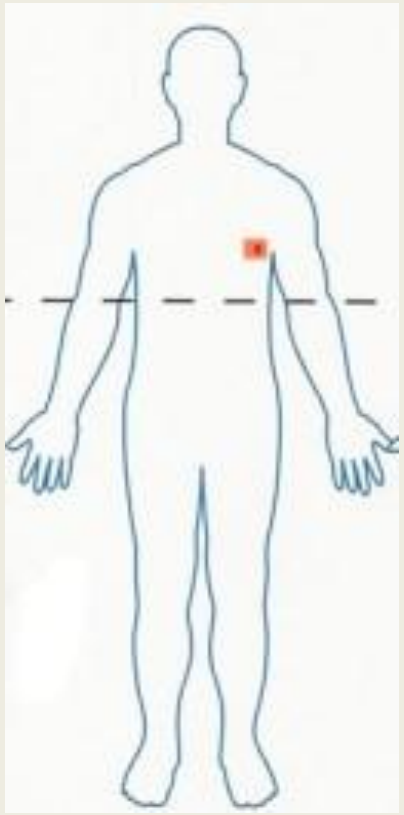
Staging of Hodgkin's Lymphoma

- **Stage I:** Involvement of single L.N. group (I) or involvement of one extranodal organ or site (I_E).
- **Stage II:** Involvement of two or more L.N. groups on the same side of the diaphragm alone (II), or with involvement of limited contiguous extra nodal organ or tissue (II_E).

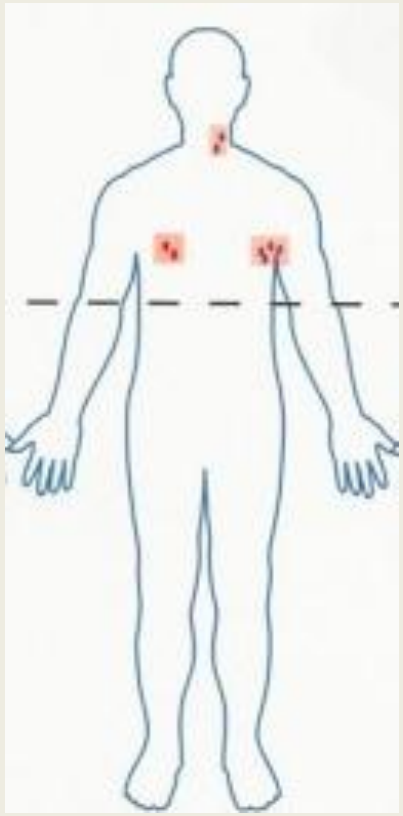
- **Stage III:** Involvement of L.N. groups on both sides of the diaphragm(III), which may include spleen (III_s) and/or limited contiguous extra nodal organ or tissue (III_E).
- **Stage IV:** Involvement of multiple or disseminated foci of one or more extra nodal organs or tissues with or without lymphatic involvement.

Hodgkin`s Lymphoma

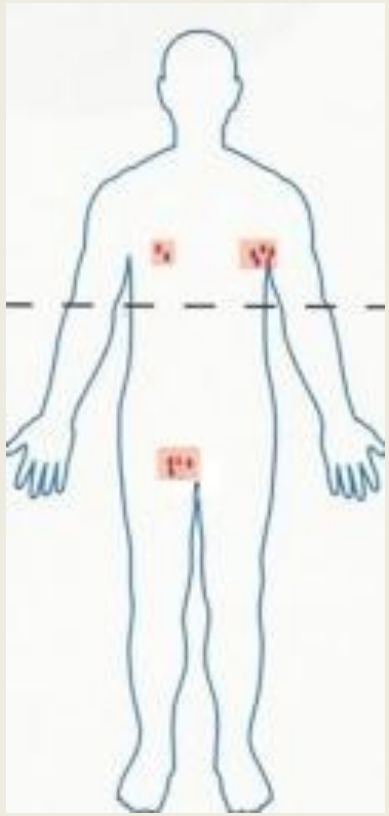
- **Clinically**:
  - Clinical staging (Ann-Arbor staging)



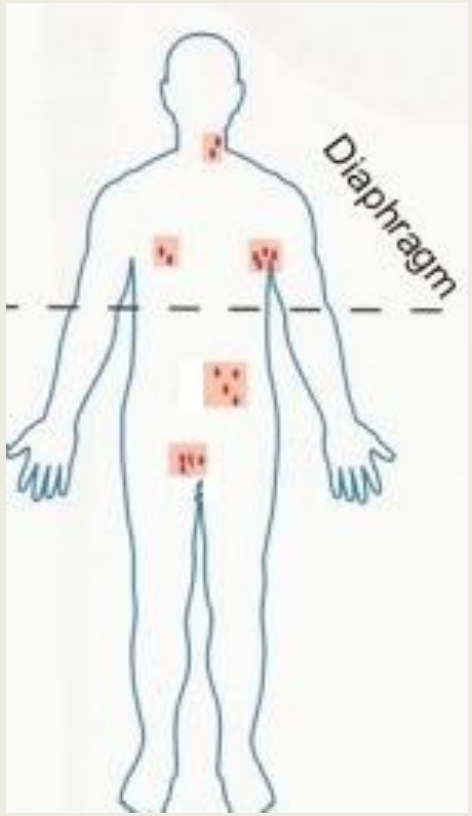
Stage I
Single LN group



Stage II
Two groups on one side of diaphragm



Stage III
LN groups on both sides of diaphragm



Stage IV
Extranodal extention

Non Hodgkin's Lymphoma

- It is diverse group of neoplastic disorders of lymphoid cells occurring in any stage of B or T cell differentiation.
- It also may arise from nodal or extranodal lymphoid tissue.

- **Special features of non Hodgkin's lymphoma (NHL):**
- Non Hodgkin's lymphoma, compared with Hodgkin's lymphoma, have the following characters:

1. They are multiple heterogeneous diseases.
2. Malignant lymphoid cells are a majority in the lesion.
3. Peripheral lymph node affection.
4. Noncontiguous lymph node spread.
5. Common primary extranodal presentation.

6. Frequent involvement of Waldeyer's ring, mesenteric lymph nodes and early dissemination to the bone marrow.
7. Frequent leukemic association or transformation.
8. Lymphoma is commonly B-phenotype, except in Japan and in children.
9. Significant impact of histological type on treatment policy.
10. Therapeutic results are inferior to Hodgkin's lymphoma.

NHL and HL

NHL	HL
Tend to involve more than one group of LNs	often localized to a single group of LNs
More frequent involve peripheral LN groups	More frequently involve axial LN groups
Cervical, mediastinal, para-aortic can be involved	Cervical, mediastinal, para-aortic are commonly involved
Mesenteric nodes and Waldeyer ring are commonly involved.	Mesenteric nodes and Waldeyer ring are rarely involved.
Frequent peri-nodal extension	Less frequent perinodal extension
Usually non-contiguous spread.	Spread is usually by contiguity.
Involvement of extra-nodal sites is common.	Involvement of extra-nodal sites is uncommon.

- **Gross:** the L.Ns. Are enlarged, soft, (commonly described as fish flesh), and pale grey in color. However, they may be firm if there is an associated fibrosis.
- **Microscopic:** it is characterized by replacement of nodal architecture by neoplastic cell population which is monoclonal either B or T cell origin.
- **Immunohistochemistry:** B cells are positively stained by CD20 antibody, while T cells are positively stained by CD3 antibody.

- **Classification (microscopic subtypes):**
- Several classifications are applied to NHL.
- Most classifications are based on the assumption that lymphoma cells are the malignant counterparts of benign lymph nodal cells.
- The various lymphomas are often named after the benign cell from which they are assumed to be derived.

1. **Rappaport Classification:**

- It is the oldest classification which was developed before lymphoid cells were divided into B and T cells.
- **It includes:**
- Well differentiated lymphocytic lymphoma.
- Poorly differentiated lymphocytic lymphoma.
- Histiocytic lymphoma.

- **Working Formulation**
- Clinician involved in treatment of NHL do not necessarily require detailed classification and may prefer to use the National Cancer Institute International Working Formulation which was designed principally for clinical usage and related to survival.
- It was based solely on the morphology of H & E stained sections.
- The criteria are both architectural (low magnification) and cytological (high magnification):

1. **Architectural:**
   - diffuse proliferation
   - follicular proliferation
2. **Cytological:**
   A. **Nuclear outline**
      - cleaved (intended)
      - non-cleaved
   B. **Cell size**
      - small
      - large
      - mixed small and large

   • The system divides NHL into three grades; low, intermediate and high without subdivision into B and T cell types.

Non-Hodgkin`s Lymphoma

Working Formulation

Low Grade	Intermediate Grade	High Grade
Small lymphocytic	Follicular large cell	Immunoblastic
Follicular small cell	Diffuse small cells	Lymphblastic
Follicular mixed small and large cell	Diffuse mixed cell	Burkitt's lymphoma
	Diffuse large cell	

2. Kiel and Lukes and Collins classification:

- Kiel classification is popular in Europe, whereas Lukes and Collins classification is popular in the United States.
- They are the first who separate B cell and T cell lymphoma using immunologic techniques.
- The Kiel System divides lymphoma into B and T cell types as well as low and high grade categories.

- In general Low grade tumors tend to consist mainly of small cells (with the suffix-cytic) and affect adults in later life.
- Whilst high grade tumors usually consist of large cells (suffix-blastic) and can be found at almost any age.

3. Real/WHO Classification (2001):

- B-cell lymphomas
- T-cell lymphomas

4. The most recently applied classification is the **WHO in 2008**.

- The classifications relies mainly on the type of cell origin, its site (e.g. follicular center, mantle, paracortex, or medulla) as well as its functional variety (e.g. B or T cells).

Origin of Lymphoid Neoplasm

Central lymphoid tissue	Peripheral lymphoid tissue			
Precursor B and T cells	**Peripheral mature B cells**			**Peripheral T cells**
Bone marrow (B) Thymus (T)	Mantle area	Follicular area	Marginal area	paracortex
Precursor B/T cell lymphoblastic leukemia/ lymphoma Multiple myeloma (B cell)	Mantle zone lymphoma	Follicular lymphoma Burkitt lymphoma DLBCL Hodgkin's lymphoma	DLBCL Marginal zone lymphoma Small lymphocytic lymphoma	Peripheral T cell lymphoma

WHO classification of selected types of NHL

B cell lymphoma	T cell lymphoma
B cell precursor lymphoma B cell leukemia/ lymphoma **Mature B cell lymphoma** Follicular Small lymphocytic Lyphoplasmocytic • Marginal zone B cell lymphoma • Extra nodal (Malt lymphoma) Mantle cell Diffuse large B cell lymphoma (DLBCL) Burkitts lymphoma	**T cell precursor lymphoma** T cell leukemia/ lymphoma **Mature T cell lymphoma** Peripheral T cell lymphoma Anaplastic large cell lymphoma (ALCL) Mycosis fungoides.

I. Precursor B and T Lymphocytes:

- Lymphocytic lymphoblastic lymphoma (T or B cell type):
- Occurs in children.
- May be associated with lymphoblastic leukemia.

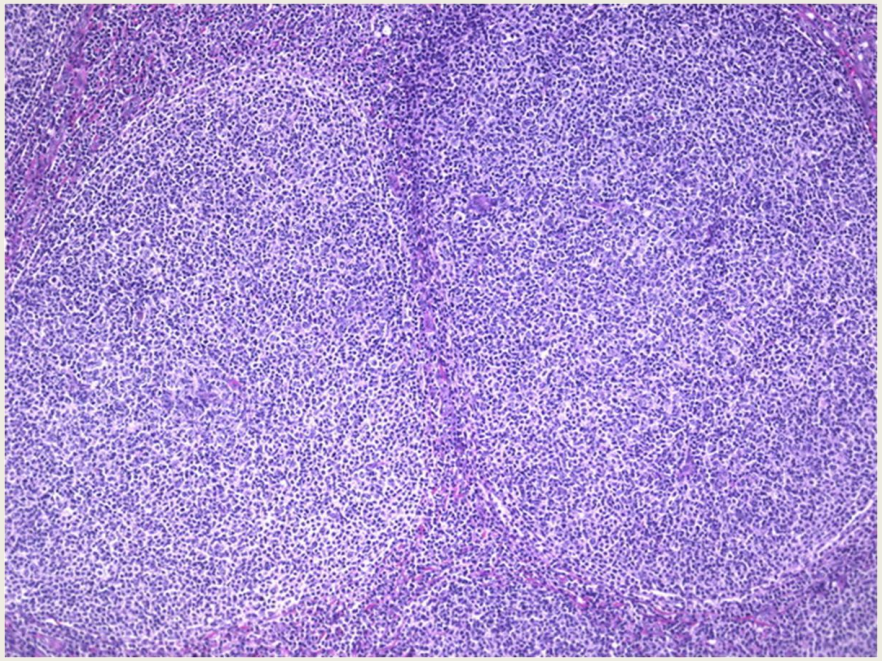
II. B cell lymphoma:

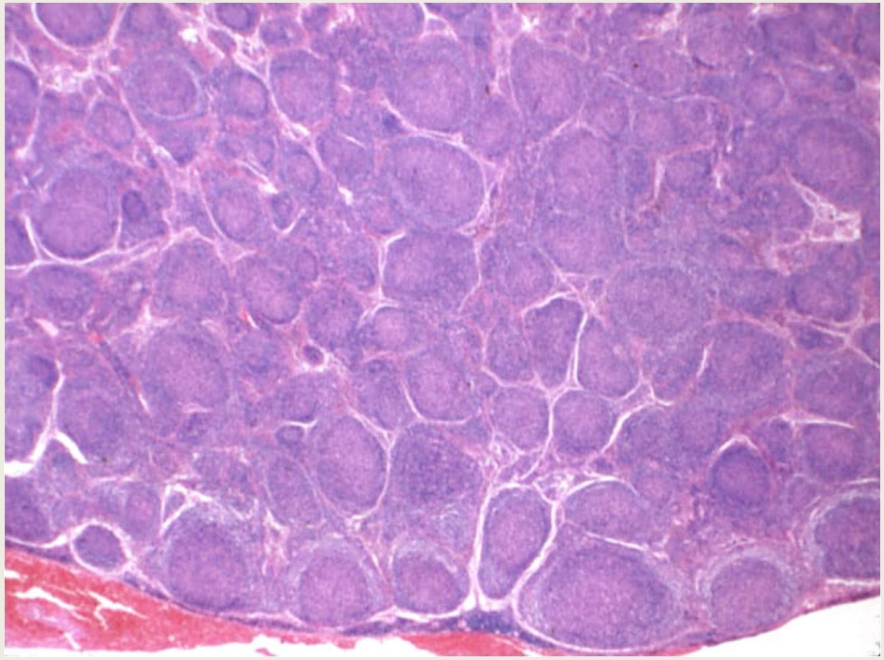
1. Follicular lymphoma:

- **Origin:** from the follicle center cells (small centrocytes and large centroblasts).
- The neoplastic cells are arranged in follicular (nodular) pattern trying to recapitulate the normal nodal follicles.

- According to the proportion of centrocytes and centroblasts forming the neoplastic follicles they are **classified into:**
- Follicular small cell type.
- Follicular mixed small and large cell type.
- Follicular large cell type.
- The predominance of centroblasts increases the grade of malignancy.

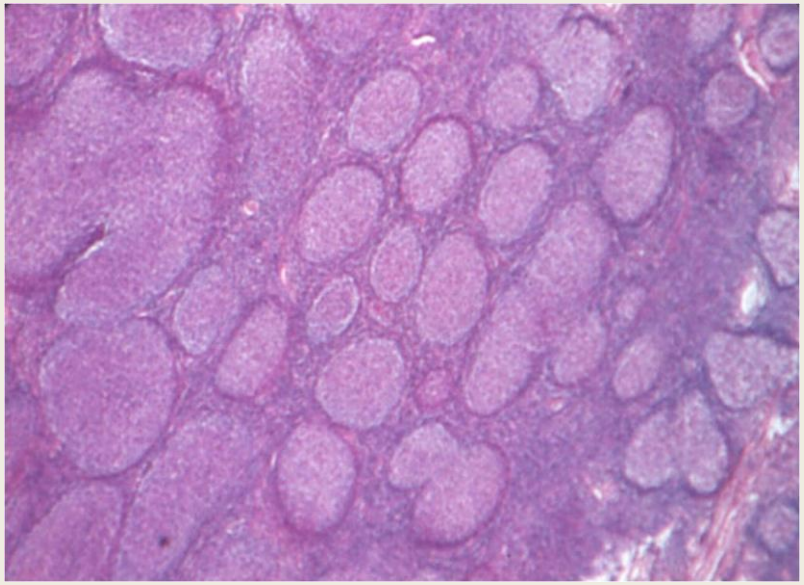
Follicular lymphoma (FL)

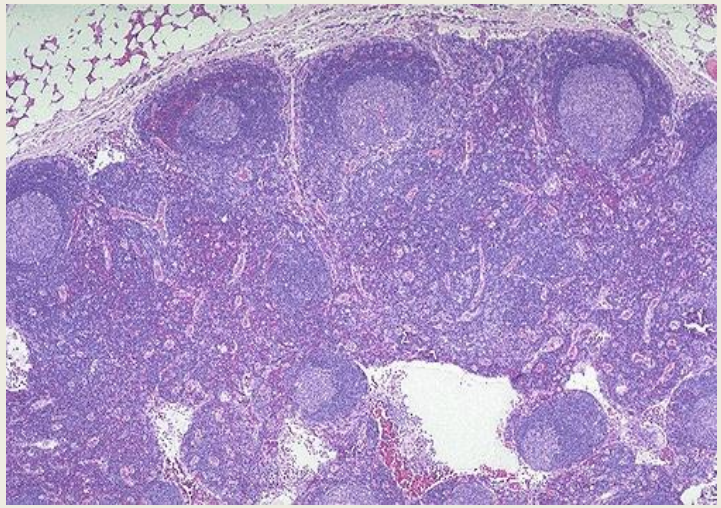


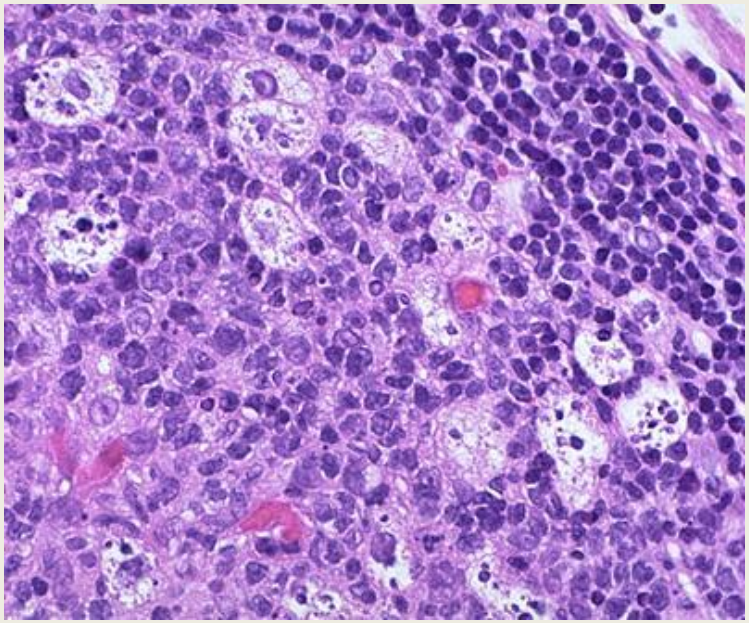


Non-Hodgkin`s Lymphoma

Follicular lymphoma (FL)







Non Hodgkin's Lymphoma

- The following table differentiates between lymphoma and reactive nodal hyperplasia:

	Reactive hyperplasia	**Follicular lymphoma**
Low power examination:	Loosely packed follicles Polymorphic follicles Prominent mantle zone	Tightly packed follicles Monomorphic follicles Absent or obscure mantle zone

	Reactive hyperplasia	**Follicular lymphoma**
Low power examination:	Polarized follicles (prominent germinal center) Preserved open sinuses No capsular invasion	Non polarized follicles (you can not detect germinal center from mantle zone) Destructed sinuses Extension into the peripheral soft tissue

	Reactive hyperplasia	**Follicular lymphoma**
High power examination:	Very high mitotic rate in germinal center Tigible body macrophages Usually paracortical lymphoid cells in between follicles	Lower mitotic rate in germinal center No tigible body macrophages Atypical cleaved cells in between follicles

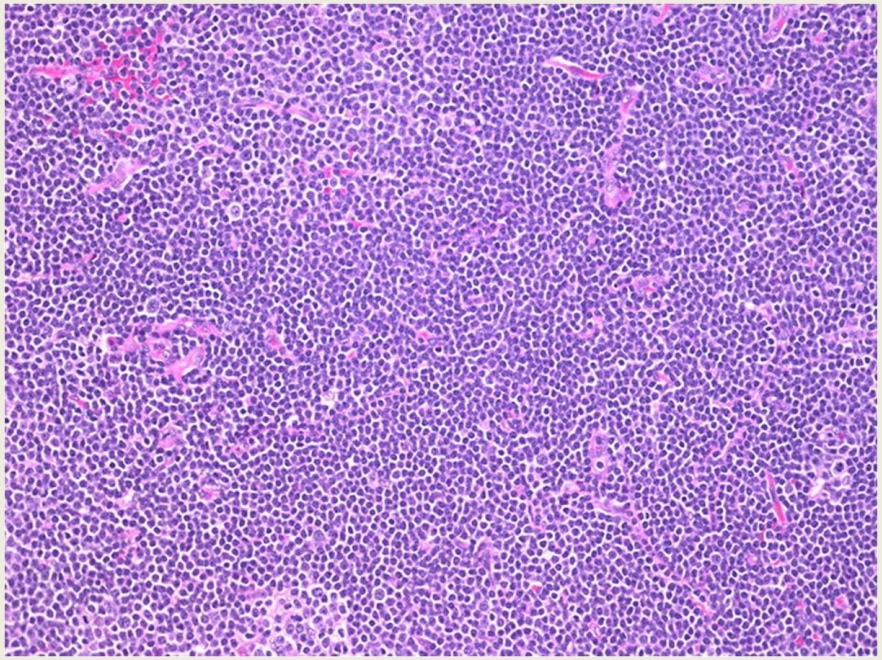
	Reactive hyperplasia	**Follicular lymphoma**
Immunohisto-chemistry (IHC)	Polyclonal light chain expression No reactivity to bcl-2 protein	Monoclonal light chain expression 85% reactivity to bcl-2 protein

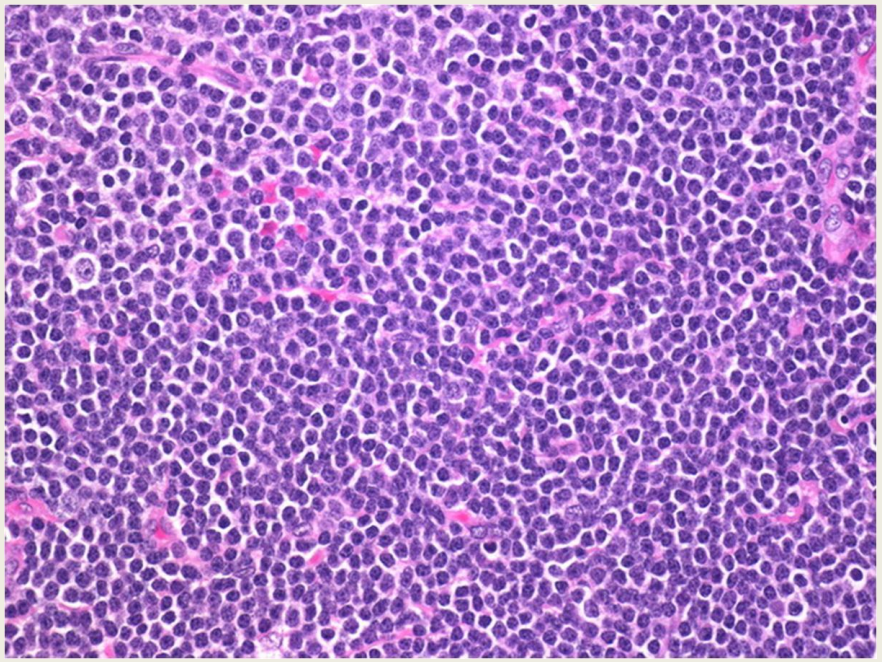
2. Diffuse small lymphocytic lymphoma:

- They occur in old age, and may be associated with chronic lymphocytic leukemia.
- **Microscopic:** there is replacement of L.N. by proliferation of uniform small lymphocytes with variable numbers of large activated cells.
- It has a good prognosis.

Low grade NHL

Diffuse small lymphocytic lymphoma (SLL)





3. Diffuse lymphoplasmocytic lymphoma:

- The neoplastic cells show plasmocytoid differentation and may secrete immunoglobulins resulting in increases blood viscosity (Waldenstorm's macroglobulinemia).

4. Mantle cell lymphoma:

- This is diffuse type of lymphoma of low grade malignancy.
- **Microscopic:** small to intermediate sized irregular lymphocytes.

5. Marginal zone lymphoma:

- This type may be nodal or most commonly in extranodal sites as the mucosa of the GIT or respiratory tract where it is called MALT (mucosa associated lymphoid tissue) lymphoma. It is low grade.

6. Diffuse large B cell lymphoma (DLBCL):

- It is the most common type of lymphoma in adults, accounting for about 40-50% of NHL and carries worse prognosis than follicular type.
- **Microscopic:** large neoplastic lymphocytes with large round or oval nuclei having prominent nucleoli.

7. Burkitt's lymphoma:

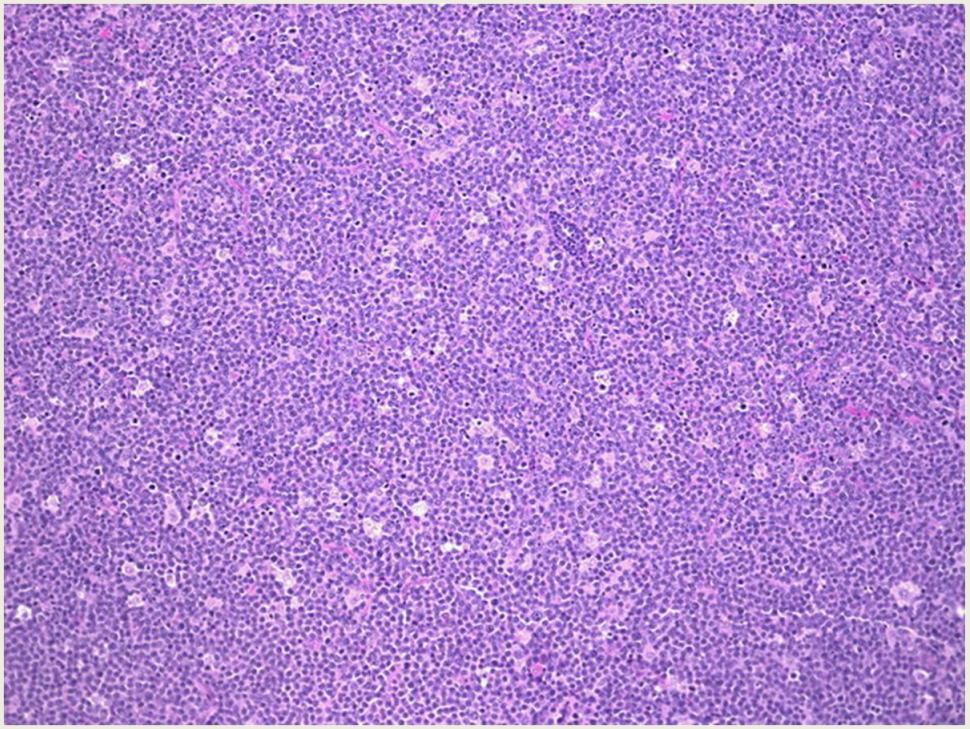
- This is a B cell tumor of diffuse pattern.
- This is commonly seen in children and rarely occurs in adults.
- It is related to Epstien-Bar virus (EBV) infection.
- **Sites: in Africans:** the bones of the maxilla and mandible are intially involved.
- **In Western countries:** it usually occurs in terminal ileum, ovaries or kidneys.
- The L.Ns. Tend to be spared in both types.

- **Microscopic:**
- Tumor cells are uniform and have round oval nuclei with 2-5 nucleoli and a rim of dense cytoplasm which contains clear lipid vacules.
- Mitotic figures are numerous. Phagocytosis of nuclear debris by macrophages is conspicuous in the rapidly dividing lymphomas with cell necrosis giving microscopic **“starry sky”** appearance.

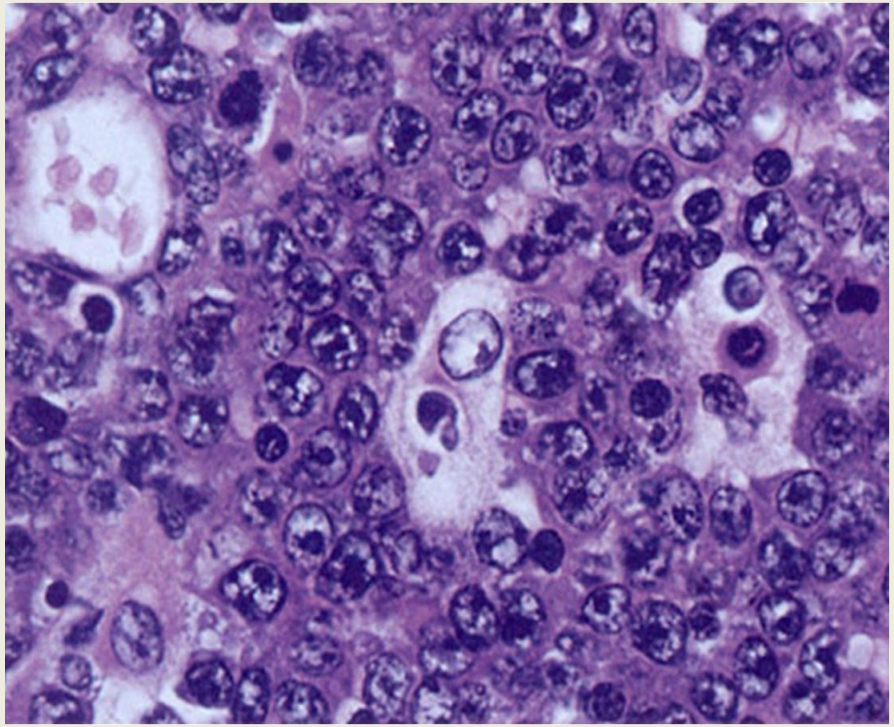
Non-Hodgkin`s Lymphoma

High-grade NHL

→ **Burkitt`s Lymphoma (BL)**



Starry-sky



III. T cell lymphoma:

- There are many types of T cell lymphoma that arise in L.Ns. and mostly present in extranodal sites.

1. Peripheral T cell lymphoma:

- Most common adult T cell lymphoma, often disseminated and aggressive.

2. Anaplastic large cell lymphoma (ALCL):

- Of high grade malignancy.

3. Mycosis fungoides:

- This is cutaneous T cell lymphoma that presents initially by a non-specific erythrodermic rash, then progress to tumor phase.

- **Microscopic:**
- The epidermis and the upper dermis are infiltrated by the neoplastic T cells.
- **Clinical picture of NHL:**
- Although each type has its own peculiar clinical picture, common clinical features are:
- Generalized or localized L.N. enlargement.
- Pressure symptoms manifested by the enlarged L.Ns. on the surrounding organs.
- Anemia and weight loss.

Causes of lymph node enlargement

- **Acute enlargement:**

1. Acute lymphadenitis
2. Infectious mononucleosis (glandular fever)
3. Typhoid fever
4. Postvaccinial lymphadenitis lymphadenitis following vaccination
5. Bubonic plaque

- **Chronic L.N. enlargement:**

1. Chronic non specific lymphadenitis
2. Granulomatous lymphadenitis as; TB, sarcoidosis, syphilis, cat-scratch disease, and Crohn's disease.
3. AIDS related lymphadenopathy i.e L.N. enlargement occurring with acquired immunodeficiency disease
4. Blood diseases especially leukemias
5. Lymphomas
6. Metastatic tumors

Diseases of the Spleen

- **Congenital anomalies:**

1. **Congenital absence (asplenia):** It is a rare condition and usually associated with congenital heart disease.
2. **Accessory spleen:** it is more common condition which may be single or multiple. It is commonly present at the tail of the pancreas or elsewhere in the abdominal cavity.

Hypersplenism

- It is a functional disorder in which the spleen is over active with increased destruction of one or more of the three cellular components of the blood by splenic macrophages resulting in one or a mixture of anemia, leucopenia, or thrombocytopenia.
- This condition may be encountered in some patients with splenic enlargement. Splenectomy is usually curative. This condition may be:

1. **Primary hypersplenism:**

- It is of unknown cause. Primary thrombocytopenia may be due to primary hypersplenism.

2. Secondary hypersplenism:

- It is more common and is usually secondary to other causes of splenomegaly as chronic venous congestion, bilharziasis, liver cirrhosis, lymphomas, leukemias, and myelosclerosis.

Congestive Splenomegaly

- Passive chronic venous congestion and enlargement of the spleen may result from:
- Systemic venous congestion encountered in cardiac decompensation involving the right side of the heart.
- Intrahepatic impairment of portal venous drainage, as occurs in fibrosis or cirrhosis of the liver.
- Obstruction of extrahepatic portal vein and splenic vein as occurs in portal or splenic vein thrombosis.

- **Gross picture:**
- The spleen is enlarged with dark brown cut surface.
- **Microscopic picture:**
- The red pulp is congested with red blood cells and become more fibrous with time. Organization of focal hemorrhages gives rise to foci of fibrosis containing deposits of iron and calcium salts (Gandy-Gamma nodules).

Neoplasms of the spleen

- Benign tumors include hemangiomas, lymphangiomas, and fibromas.
- Malignant tumors include primary tumors as lymphomas and hemangiosarcomas. Leukemic deposits also may be seen in the spleen.
- Metastasis to the spleen are not common and are usually found only in very advances malignancies.

Causes of enlargement of the spleen

1. **Infectious causes such as:**

- Non specific splenitis of various blood born infections (particularly infective endocarditis that causes acute splenic swelling)
- Typhoid fever (causes splenic swelling)
- Infectious mononucleosis
- Tuberculosis and syphilis
- Bilharziasis
- Ecchinococcosis (hydatid cyst)
- Toxoplasmosis
- Kala-azar

2. Congestive causes:

- Cirrhosis of the liver
- Portal or splenic vein thrombosis
- Right sided cardiac failure

3. Lymphohematogenous disorders:

- Lymphomas
- Leukemias
- Hemolytic anemias
- Thrombocytopenic purpura

4. Immunologic inflammatory conditions:

- Rheumatoid arthritis
- Systemic lupus erythematosis
- Storage diseases:
- Gaucher’s disease
- Nieman Pick disease
- Mucopolysarcoidosis

5. Miscellaneous:

- Amyloidosis
- Primary neoplasms and cysts
- Secondary neoplasms

Diseases of the White Blood Cells

- The bone marrow, lymph nodes and spleen are involved in hematopoiesis.
- These organs and tissues have traditionally been divided into **myeloid tissue**, which includes the bone marrow and the cells derived from it (erythrocytes, platelets, granulocytes and monocytes), and **lymphoid tissue**, consisting of thymus, lymph nodes and spleen.

- This subdivision is artificial with respect to the normal physiology of hematopoietic cells and the diseases affecting them.
- Although the bone marrow is not the site where most of the mature lymphoid cells are found, it is the source of lymphoid stem cells.
- Similarly, **leukemia**, which is a neoplastic disorder of leukocytes originates within the bone marrow but involves the lymph nodes and spleen quite prominently.

- Some red cell disorders (hemolytic anemia) result from formation of auto-antibodies, signifying a **primary disorder** of the lymphocytes.
- Thus, it is not possible to draw neat lines between diseases involving the myeloid and the lymphoid tissues.

- **Reference range for white cell count (WBC) and differential in healthy adults $X10^9/L$:**

White blood cells (WBC)	$4.0\text{-}11.0X10^9$
Granulocytes	
Neutrophils	$2.5\text{-}7.5X10^9$
Eosinophils	$0.04\text{-}0.44X10^9$
Basophils	$0\text{-}0.1X10^9$
Lymphocytes	$1.5\text{-}3.5X10^9$
Monocytes	$0.2\text{-}0.8X10^9$

Variations in white blood cell counts

- **Leucocytosis**
- Increased in total leucocytic count above $11X10^9/L$.
- The commonest cause of neutrophil leucocytosis is bacterial infection usually in the range of 15-25 $X10^9/L$.

- Moderate increase also occur in connective tissue diseases and necrosis, e.g. in myocardial infarction, burns, bone marrow neoplasia e.g. polycythemia vera, rapidly occurring tumors undergoing ischemic necrosis.
- Transient neutrophil leucocytosis develops within few hours of hemorrhage, and in acute hemolysis.
- In bacterial infection immature forms, metamyelocytes and myelocytes may be found in the circulation.

- An exaggerated form of this with circulating myeloblasts, a **“leukemoid reaction”** may mimic leukemia.
- A leukemoid reaction may also occur with severe hemolysis and as a paraneoplastic reaction to some tumors.
- The neutrophil alkaline phosphatase is high in contrast to chronic granulocytic leukemia.

- **Causes of lymphocytosis:**

1. Acute infection: whooping cough
2. Chronic infection e.g. tuberculosis and syphilis
3. Infectious mononucleous

- **Eosinophilia: is observed in:**

1. Infestation by parasites as bilharziasis, trichinosis, and hydatid disease
2. Allergic states as asthma

- **Monocytosis:** In tuberculosis, typhus, malaria, subacute bacterial endocarditis and infectious mononucleosis.

- **Leucopenia**
- Reduction of the total leucocytic count below $4X^9/L$.
- **Causes:**

(1) Decrease formation in:

a. Toxemia: e.g. typhoid, influenza and miliary tuberculosis.

b. Septicemia.

c. Toxic drugs and chemicals as barbiturate, sulfanilamide, and chloramphenicol.

d. Aplastic and myelophthisic anemia.

e. Deficiency of folic acid and BI2.

f. Excess bone irradiation.

(2) Increase destruction of the leucocytes in hypersplenism.

- **Agranulocytosis:**
- Decrease in the total leucocytic count below 1^{9}/L.
- Lymphocyte is the dominant leucocyte in the blood.
- May be a part of bone marrow aplasia or occurs separately.
- It is of bad prognosis and fatal

- **Characterized by marked decrease in resistance that leads to:**

1. Severe infection as bronchopneumonia
2. Agranulocytic angina with severe ulceration of mucous membrane. Necrotizing and ulcerating lesions mainly in the mouth, pharynx, rectum and vagina, sometimes in the kidney, bladder and lungs.

- **Causes:**

1. Viruses
2. Chemical agents as benzene
3. Ionizing radiation
4. Congenital chromosomal abnormalities

Leukemia

- It is a malignant proliferation of the white cell series in the bone marrow i.e. leucoblastic series. This leads to a marked increase in total white cell count with the appearance of immature cells both in the peripheral blood and tissues of the body.
- Rarely, the white cell count is normal or low, but immature series are invading the peripheral blood, this is called aleukemic leukemia.

- **Classifications:**

1. **Chronic leukemia:**
    a. Myeloid (myelocystic)
    b. Lymphatic (lymphocytic)
2. **Acute leukemia:**
    a. Myeloid (myeloblastic)
    b. Monocytic (monoblastic)

Chronic Leukemia

A. Chronic myeloid leukemia:

- **Hematological finding:**
- **Total white cell count:**

1. Markedly increased reaching up to 800,000/cmm.

- There are PMN leucocytosis with many myelocytes and metamyelocytes and few meloblasts.

2. Increased eosinophils and basophils with their myelocyte precursors.

3. RBCs show late normochromic, normocytic anemia due to hemolytic process or inadequecy of BM.
4. Blood platelets show late thrombocytopenia
5. Bone marrow is hypercellular and leucoblastic

- **Pathological findings:**

1. Spleen:

- **Gross:** markedly enlarged, dark in color, and shows infarction due to leukemic thrombi.
- **Microscopic:** the lymphoid follicles are atrophied.
- The red pulp is infiltrated with leukemic cells i.e., myelocytes and myeloblasts with areas of myeloid metaplasia.

2. **Liver:** is enlarged due to diffuse infiltration of the portal tracts and siusoids with leukemic cells
3. **L.Ns.:** show late affection.
4. **Other organs** can also be affected
5. **Anemia with fatty change:** in parenchymatous organs
6. **Thrombocytopenia** leading **hemorrhage**

- PMLs are increased in number, yet are enable to perform their function as phagocytes resulting in **secondary bacterial infection**.

B. Chronic lymphocytic leukemia:

- It is commonly occurring in adult.
- **Hematological finding:**

1. The total white cell count is raised between 20,000 up to 250,000 cells/cmm. About 90% of these cells are mature lymphocytes with some lymphoblasts.
2. The red blood cells show normocytic normochromic anemia.
3. The blood platelets: moderate thrombocytopenia
4. The bone marrow shows late absolute increase in lymphocytic series.

- **Pathological findings:**

1. **L.Ns.** show marked generalized enlargement with diffuse infiltration by lymphocytes, a picture resembling malignant lymphoma.
2. The **spleen** is slightly enlarged with hyperplastic lymphoid follicles.
3. The **liver** is enlarged due to leukemic infiltration mainly in portal tracts.
4. **Skin and mucous membranes:** show nodules of leukemic cells.
5. **Anemia** with fatty change, hemorrhages, and secondary bacterial infection, similar to those occurring in chronic myeloid leukemia.

- Fate of chronic leukemia:
- Untreated cases are invariably fatal within 1-5 years.
- Chronic myeloid leukemia is more rapidly fatal, where the cause of death is acute exacerbations.
- Chronic lymphocytic leukemia has a slower course with up to 10 years survival and the cause of death is intercurrent infection.

	Chronic Myeloid Leukemia	**Chronic Lymphocytic Leukemia**
Age	20-40 years	40-60 years
Predominant cell	Myelocytes & leucocytes	Lymphocytes
Lymph nodes	Slight enlargement	Marked enlargement
Spleen	Marked enlargement Frequent infarcts	Moderate enlargement Less frequent infarcts
Liver	Moderate to marked enlargement	Slight enlargement

Acute Leukemia

- It occurs more commonly in children and young adults and in old age.
- It runs a rapid and fulminating course.
- The disease is heralded by high remittent fever, rapid anemia, bleeding manifestations, necrotic lesions of the mouth and throat with some enlargement of L.Ns., spleen and liver.

- **Hematological findings:**

1. The white blood cell count is moderately raised up to 100,000cells/cmm. Most of the cells are immature or blast cells with very few mature cells.
2. Marked normocytic normochromic anemia.
3. Thrombocytopenia.