Lymphoreticular system pathology

lecture 1

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General introduction

- **The components of the hematopoietic system have been traditionally divided into:**

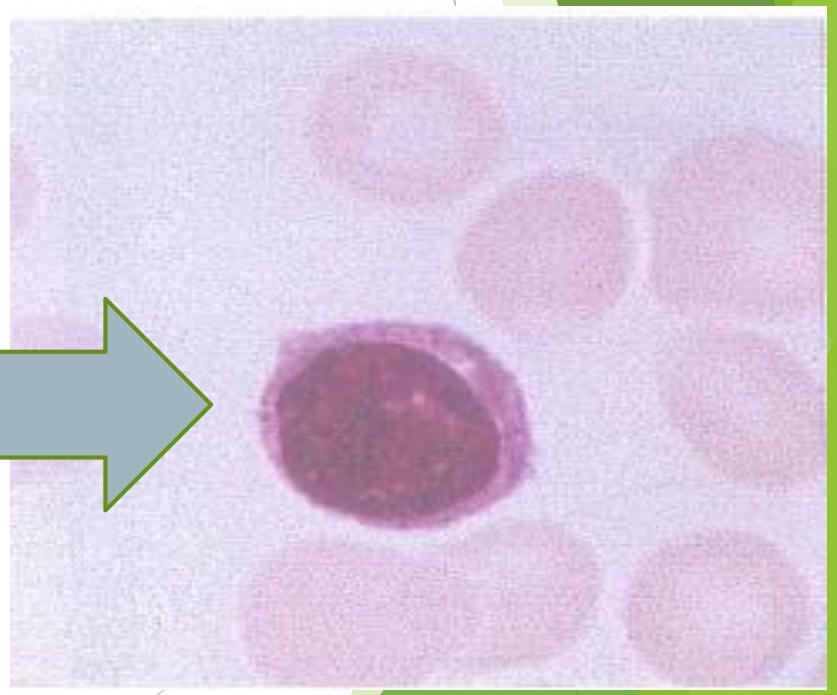
1. **Myloid tissues: includes bone marrow and the cells derived from it (red cells, platelets, granulocytes, and monocytes).**
2. **lymphoid tissues: consisting of the thymus, lymph nodes, and spleen.**

Bone marrow also is the home for all lymphoid progenitors

- **This division is artificial because disorders affecting one component might affect the other (myloid leukemia arising in the bone marrow could involve the spleen).**

- **Lymphocytes are the immunologically competent cells that assist the phagocytes in defense of the body against infection and other foreign invasions.**

Lymphocyte in blood smear



Lymphoid Organs:

***The primary lymphoid organs*:**

- **Include the bone marrow and thymus, where lymphocytes develop in the postnatal life.**

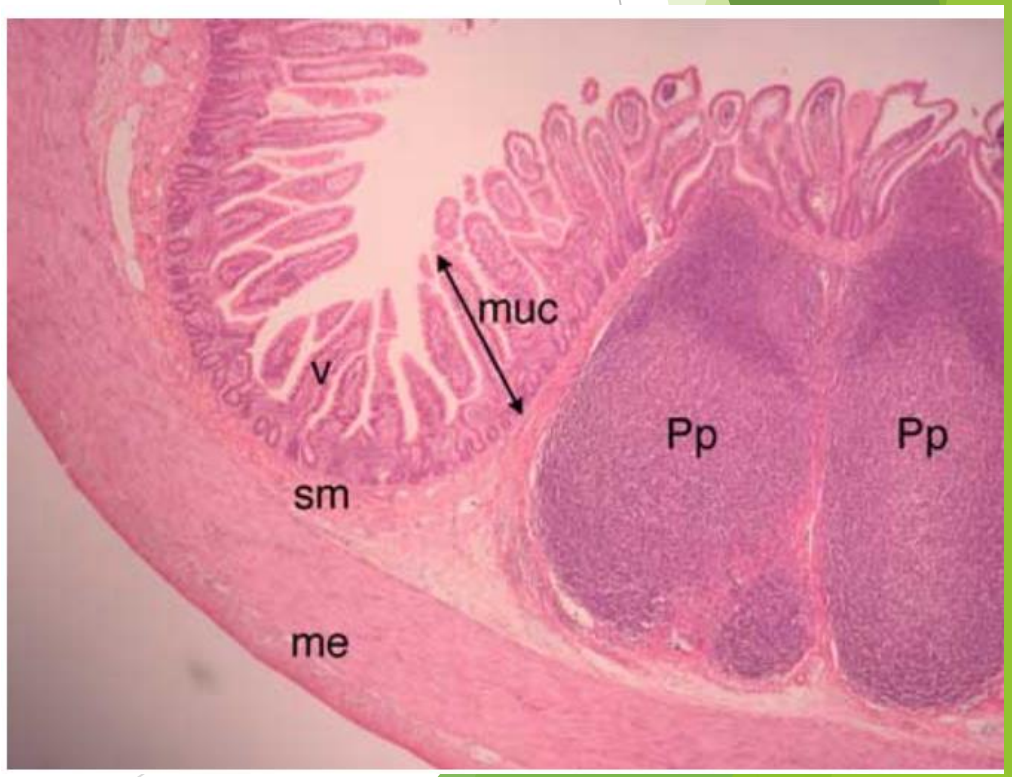
The secondary lymphoid organs

- **In which specific immune responses are generated, include the lymph nodes, spleen and lymphoid tissues of the alimentary and respiratory tracts.**

Mucosa-associated lymphoid tissue (MALT):

- Discrete lymphoid structures such as in the appendix and **Peyer's patches** in the submucosa of the intestine and the tonsils and adenoids (the latter collectively referred to as **Waldeyer's ring**) in the pharynx.

PP=Peyer's patches



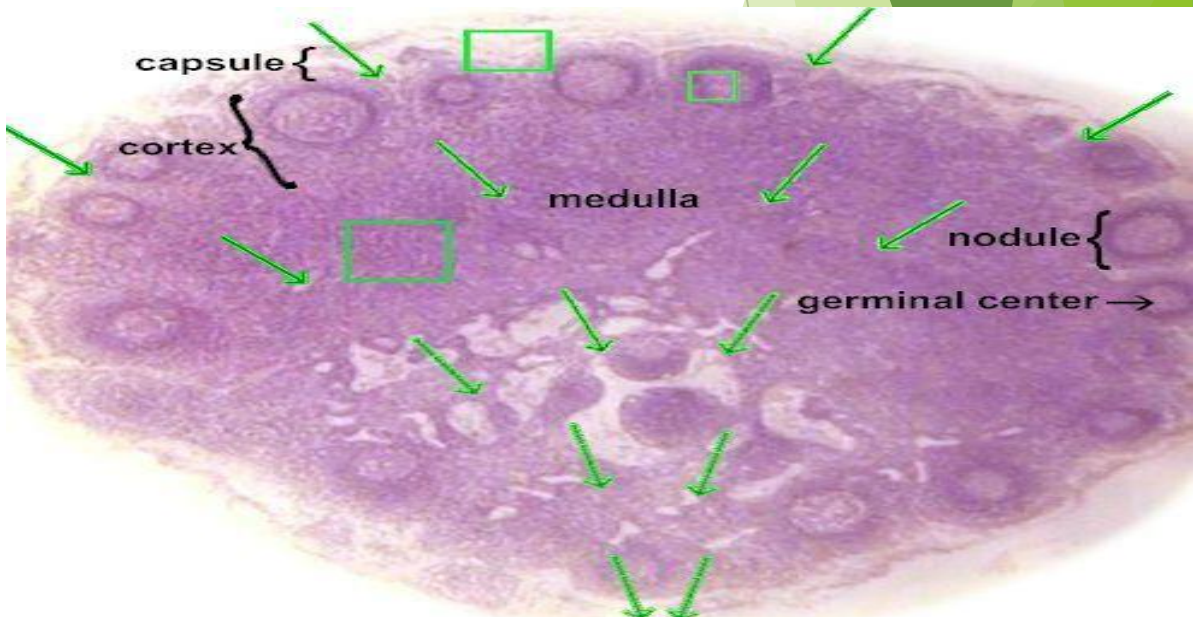
The structure of lymph node:

- **Lymph node is divided into:**

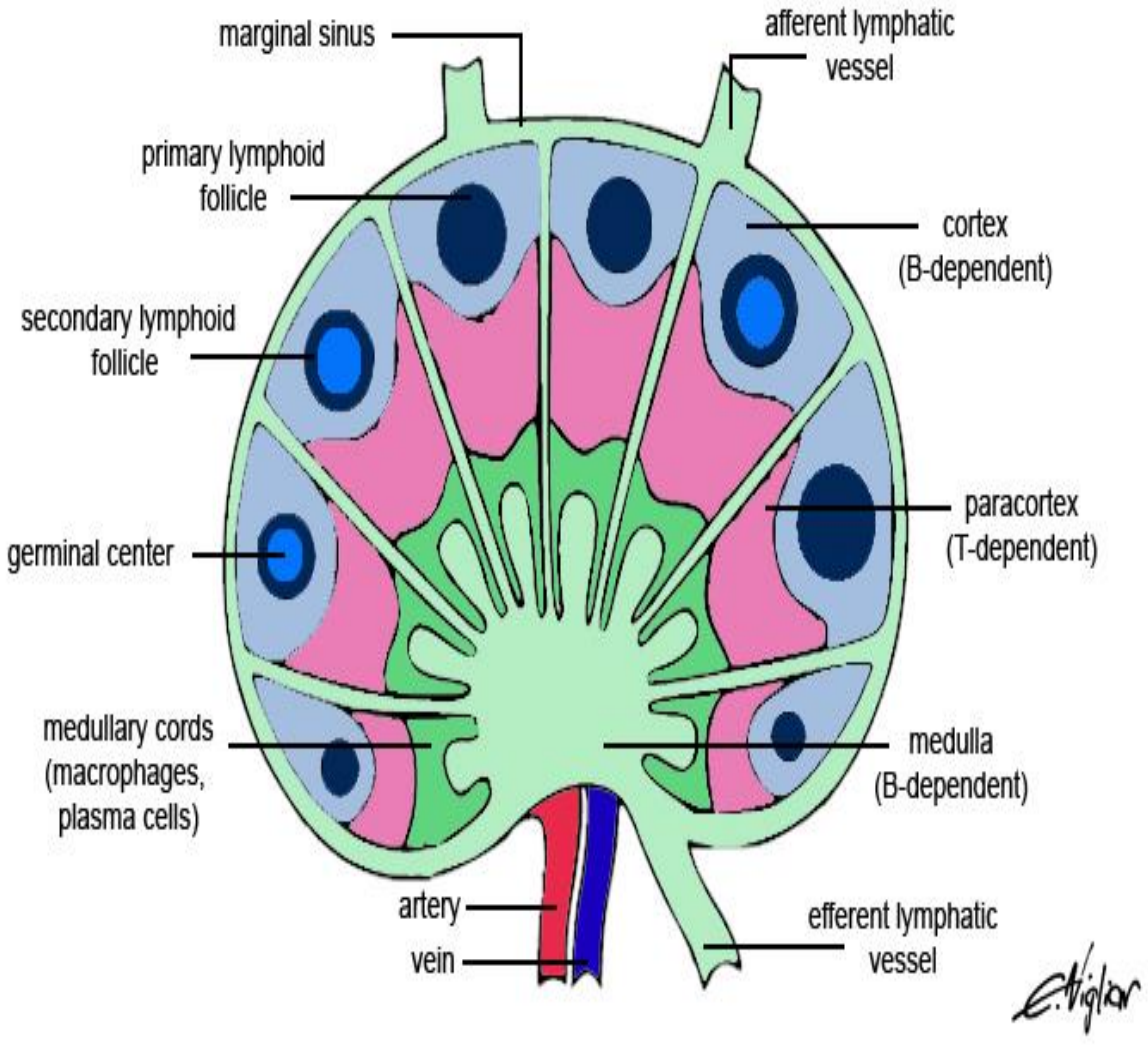
1.Cortex: Within the cortex are primary follicles, which are composed of B lymphocytes and follicular dendritic cells.

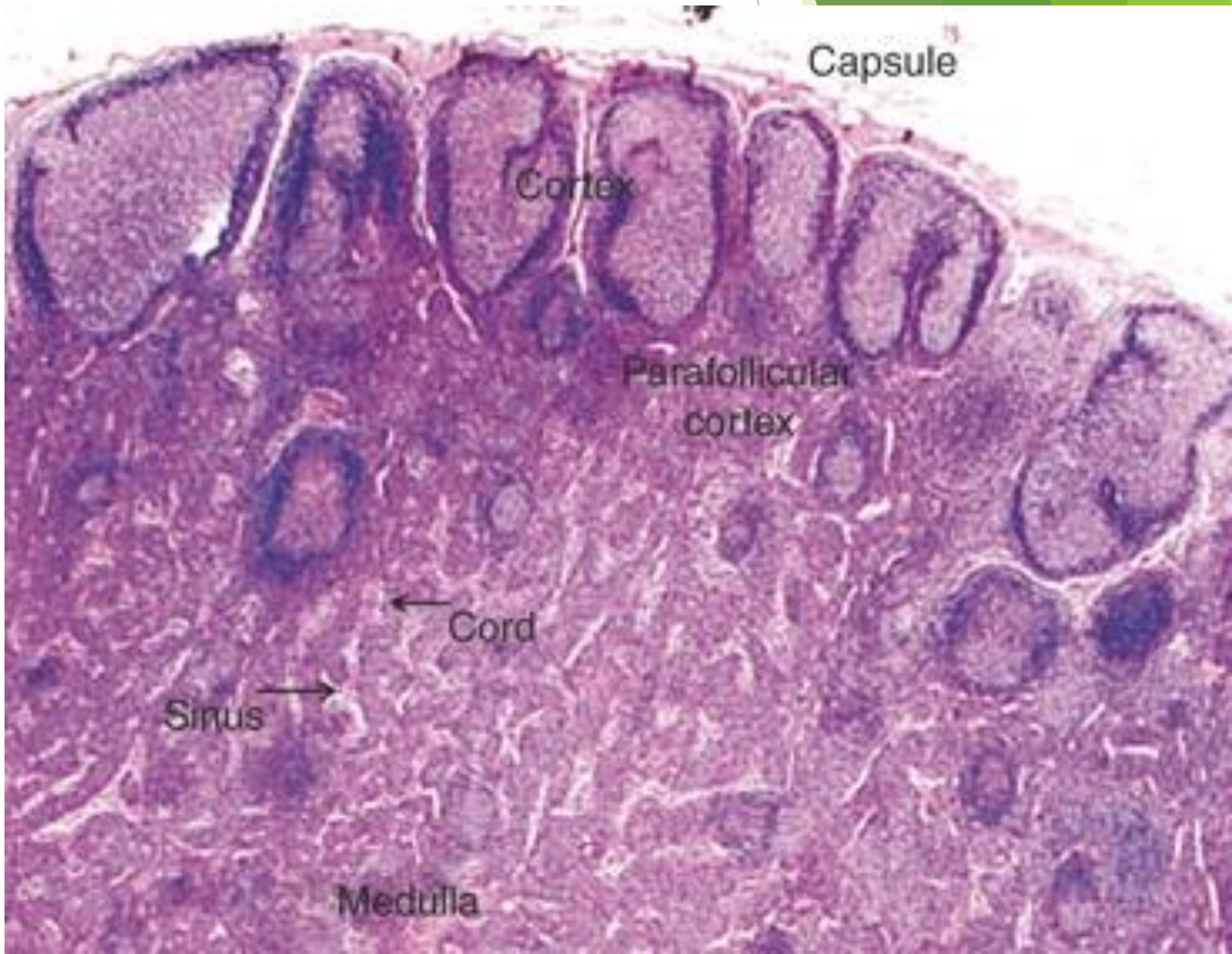
- **On antigen exposure , proliferation and maturation of B cells cause the primary follicle to develop into a secondary follicle.**

- **Secondary follicle has a germinal center surrounded by a mantle zone of small B lymphocytes.**
- **Outside the mantle zone some lymph node germinal center have a marginal zone, also composed of B lymphocytes.**



2.Paracortex :T cells occupy the paracortex, which surrounds and underlies the primary and secondary follicles. The paracortex also has abundant dendritic cells.





- 3. **Medulla.** In the center of the lymph node ,it composed of medullary cords and sinuses.

- The medullary cords are occupied by B and T lymphocytes, plasma cells and macrophages.

Classification of white cell disorders

1. **Deficiency: Leukopenias.**
2. **Proliferations: Leukocytosis, which are either:**

- Reactive : to microbial agents which are common.

- Neoplastic : less common but ominous causing 9% of all cancer deaths in adults and a staggering 40% in children younger than 15 years of age.

NONNEOPLASTIC DISORDERS OF WHITE CELLS

- **Leukocytosis: An increase in the number of white cells in the blood.**

- **Leukocytosis is non-specific and often classified according to the particular white cell series that is affected(Neutrophilic Leukocytosis, Eosinophilic Leukocytosis, Monocytosis and Lymphocytosis).**

- **In some cases reactive leukocytosis may mimic leukemia and termed as *"leukemoid reactions", this is occurring in two major situations: viral infections in children and in severe infections with release of immature WBC from bone marrow.***

Causes of lymphocytosis

1.Infections

- ***Acute :*** ***infectious mononucleosis, rubella, pertussis,*** **mumps, infectious hepatitis, cytomegalovirus, HIV, herpes simplex or zoster.**

- ***Chronic :*** ***tuberculosis, toxoplasmosis, brucellosis,*** **syphilis.**

2.Chronic lymphoid leukaemia .

3.Acute lymphoblastic leukaemia

4.Non-Hodgkin's lymphoma (some)

Lymphopenia :

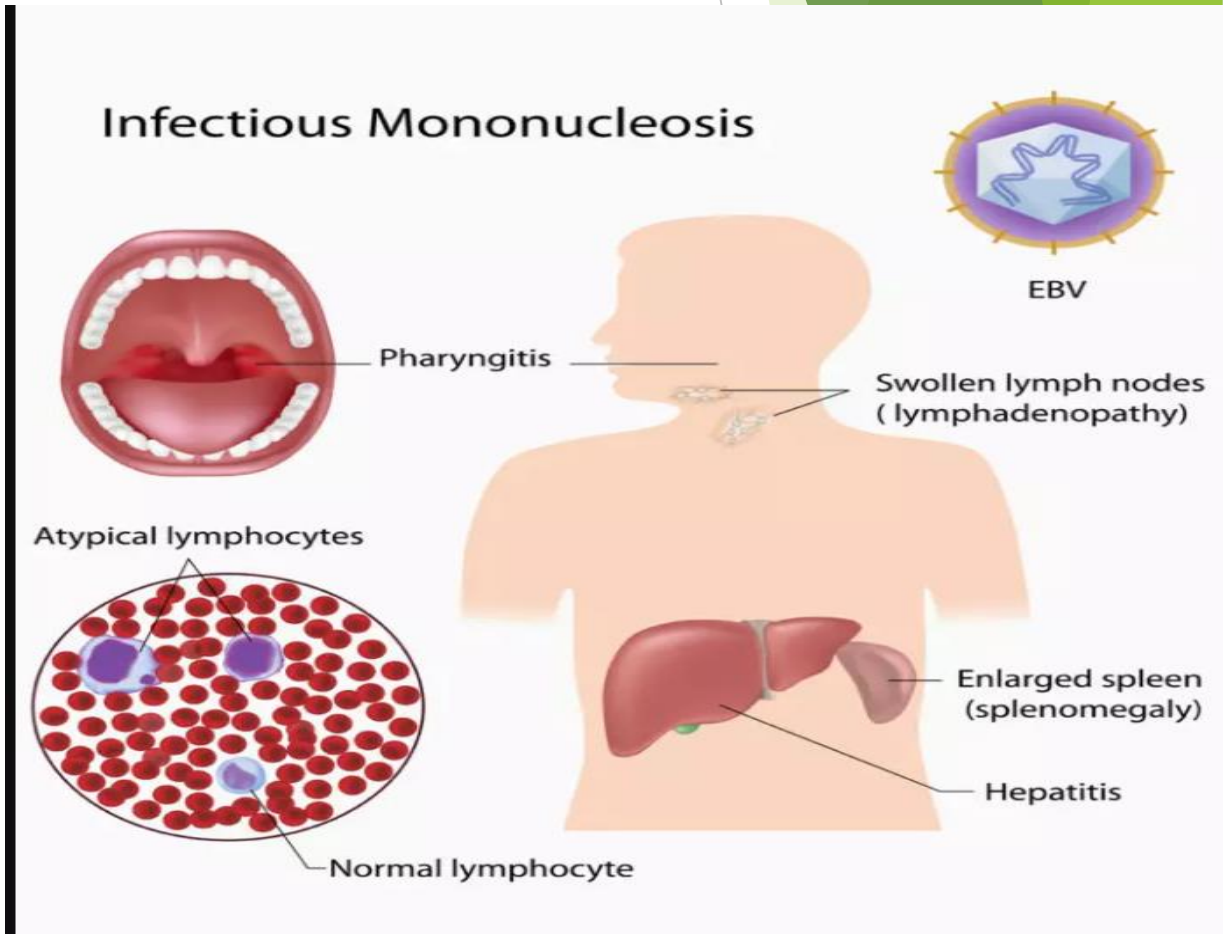
lymphopenia : it is a reduced lymphocyte count.

occur in :

1. **severe bone marrow failure.**
2. **corticosteroid and other immunosuppressive therapy.**
3. **Malnutrition**
4. **certain acute viral infections..**
5. **widespread irradiation.**
6. **immunodeficiency syndromes, the most important of which is HIV infection .**

Infectious Mononucleosis (Glandular fever)

- **an acute, self-limited disease of adolescents and young adults that is caused by Epstein-Barr virus (EBV) and other viruses like CMV.**
- **Characterized by:-**
- (1) fever, sore throat and generalized lymphadenitis
- (2) a lymphocytosis of activated, CD8+ T cells.



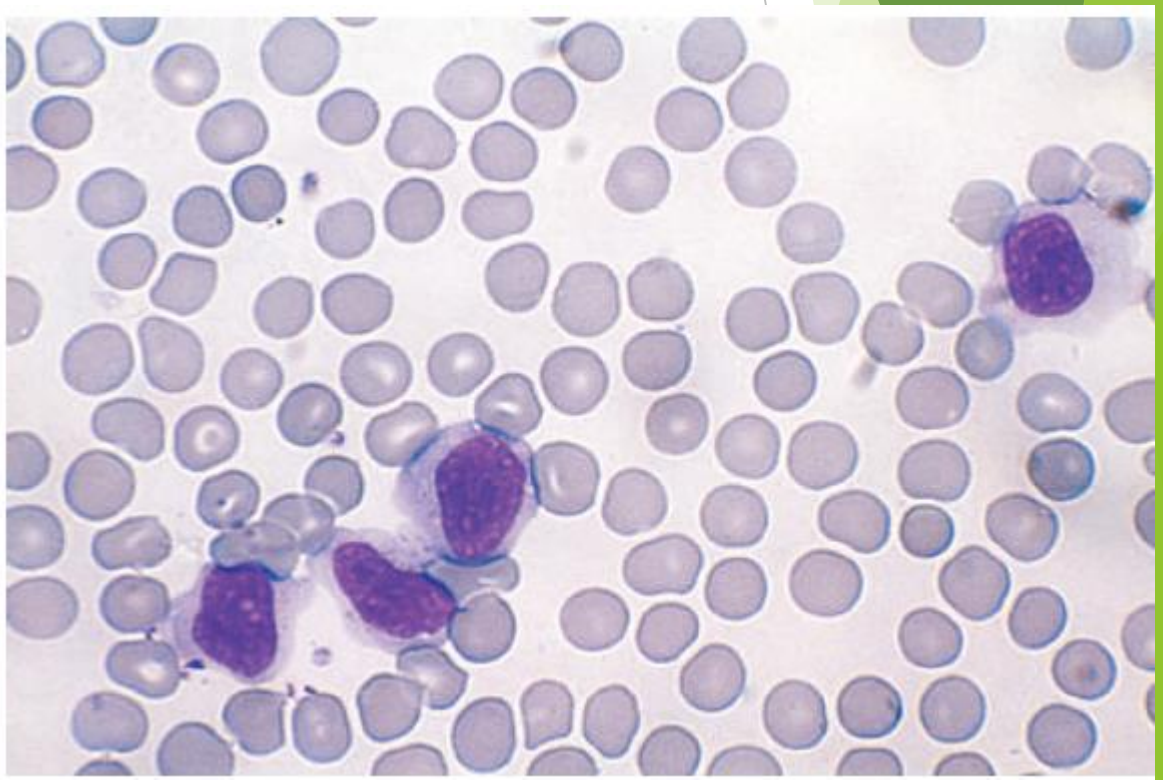
Pathogenesis

- EBV is **ubiquitous** in all human populations.
- In developing countries infection occur early in life and usually asymptomatic.
- In developed countries occur at adolescence and usually symptomatic.
- Transmission to a seronegative "kissing cousin" usually involves direct oral contact.
- virus initially infects oropharyngeal epithelial cells and then spreads to underlying lymphoid tissue (tonsils and adenoids), mature B cells are infected and majority proliferate.
- Early in the course of the infection, **IgM** antibodies are formed against viral capsid antigens. Later the serologic response shifts to **IgG** antibodies, which persist for life.

Infectious mononucleosis pathogenesis-continue

- More important in the control of the EBV-positive B cell proliferation are cytotoxic CD8+ T cells.

- Virus-specific CD8+ T cells appear in the circulation as **atypical lymphocytes**, a finding that is characteristic of mononucleosis.



Diagnosis of IM

- **The diagnosis depends on the following findings: In increasing order of specificity:**

1. lymphocytosis with the characteristic atypical lymphocytes in the peripheral blood. (WBC count of 12,000 and 18,000 cells/μL, **atypical lymphocytes** are 12 to 16 μm in diameter, with an oval, indented, or folded nucleus and abundant cytoplasm.

2. a positive heterophile reaction (monospot test).

3. a rising titer of antibodies specific for EBV antigens **.**
4. In atypical cases (only fever or only lymphadenopathy…etc) biopsy of lymph node is indicated to differentiate from lymphoma.

prognosis

- **In most patients, mononucleosis resolves within 4 to 6 weeks.**
- Occasionally, one or more complications develop:- Perhaps the most common of these is **hepatic dysfunction**(the virus produce hepatitis).
- Other complications involve the nervous system, kidneys, bone marrow, lungs, eyes, heart, and spleen(**splenic rupture** can occur due to splenic enlargement).
- **EBV is a potent transforming virus that plays a role in the pathogenesis of a number of human malignancies**, including several types of B cell lymphoma(if there is impairment of T-cell immunity).

Reactive Lymphadenitis:

- Any immune response against foreign antigens is often associated with lymph node enlargement **(lymphadenopathy)** .
- The infections that cause lymphadenitis are numerous and varied and may be acute or chronic.
- In most instances, **the histologic appearance of the nodes is entirely nonspecific. (however patterns of reaction seen and can give clues).**
- A somewhat distinctive form of lymphadenitis that occurs with cat-scratch disease is described separately later.

Causes of Lymphadenopathy :

Localized	Generalized
local infection • pyogenic infection, e.g. pharyngitis, dental abscess, otitis media, • viral infection • cat scratch fever • lymphogranuloma venereum • tuberculosis ***lymphoma*** • Hodgkin's lymphoma • non-Hodgkin's lymphoma ***Carcinoma (secondary)***	***Infection*** • viral, e.g. infectious mononucleosis, measles, rubella, viral hepatitis, HIV • bacterial, e.g. syphilis, brucellosis,tuberculosis, *Salmonella,* • fungal, e.g. histoplasmosis • protozoal, e.g. toxoplasmosis ***Non-infectious inflammatory diseases***, e.g. sarcoidosis, rheumatoid arthritis, SlE, other connective tissue diseases, ***Malignant*** • leukaemias • lymphoma: non-Hodgkin's lymphoma, Hodgkin's lymphoma ***Miscellaneous*** • reaction to drugs and chemicals, e.g. hydantoins, beryllium • hyperthyroidism

Acute Nonspecific Lymphadenitis

- This form of lymphadenitis may be isolated to a group of nodes draining a local infection, or be generalized, as in systemic infectious and inflammatory conditions
- ***Macroscopically*** : reactive nodes are swollen gray-red

- ***Microscopically*** : there are **large germinal centers** containing numerous mitotic figures.
- When the cause is a pyogenic organism, **a neutrophilic infiltrate** is seen.
- With severe infections, there **is necrosis and abscess formation.**
- The overlying skin is frequently red, and sometimes penetration of the skin can produce **draining sinuses**.
- With control of the infection, the lymph nodes can revert to their normal appearance or, if damaged by the immune response, undergo ***scarring.***

Chronic Nonspecific Lymphadenitis :

- This condition can assume one of three patterns, depending on the causative agent:

- **follicular hyperplasia.**

- **paracortical hyperplasia.**

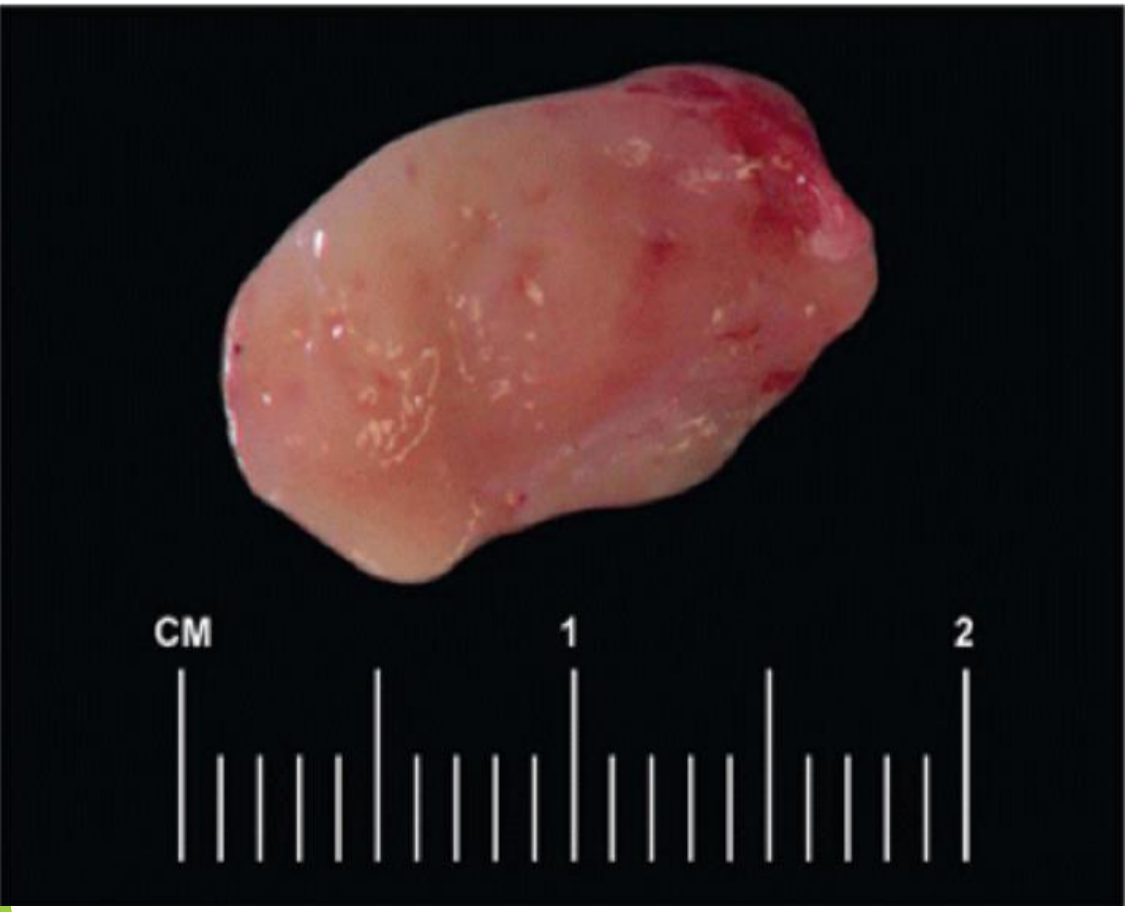
- **sinus histiocytosis**.

1-Follicular hyperplasia:

- **is associated with infections or inflammatory processes that activate B cells which migrate into B cell follicles and create the follicular (or germinal center) reaction.**

The cells in the reactive follicles include:

- the activated B cells (called follicular center cells).
- scattered phagocytic macrophages containing nuclear debris (tingible body macrophages).
- meshwork of antigen-presenting follicular dendritic cells.
- Causes include **Rheumatoid arthritis, Toxoplasmosis, and the early stages of HIV infection.**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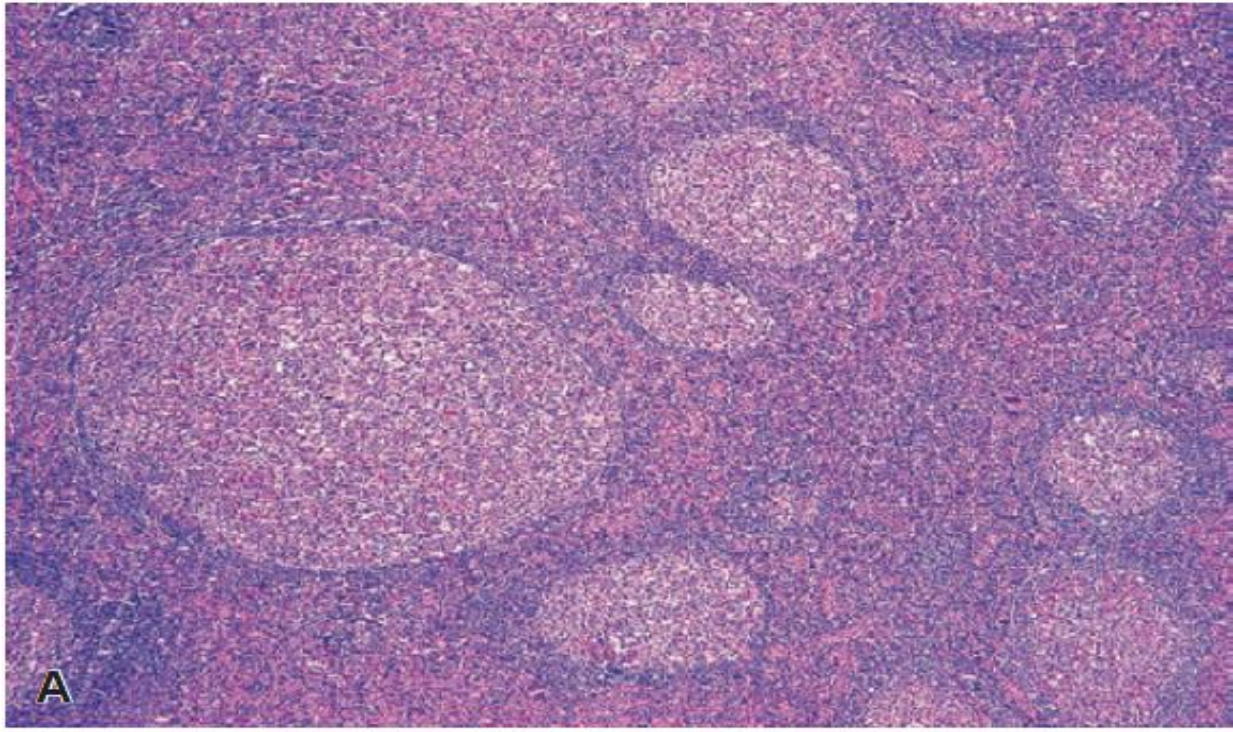
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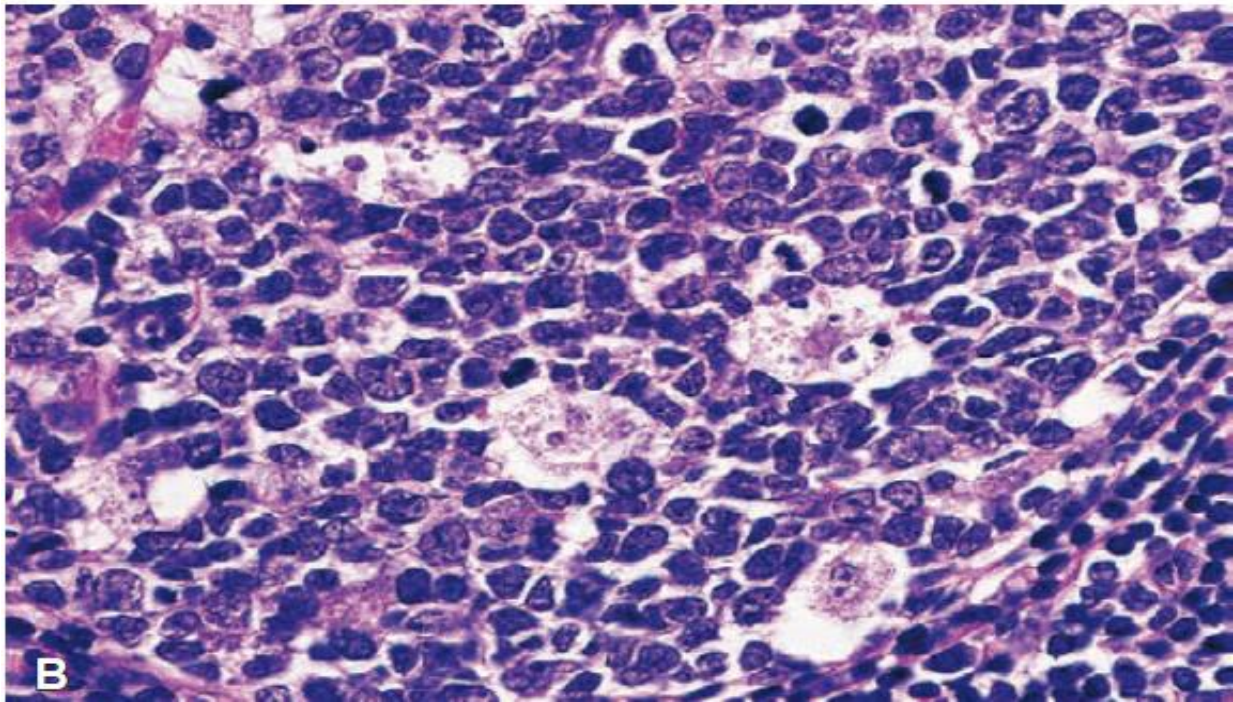
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2-Paracortical hyperplasia:

- **caused by immune reactions involving the T cell regions of the lymph node, which is reflected microscopically as expanded zones between the cortical follicles.**

- **Paracortical hyperplasia is encountered in: Viral infections (such as EBV), Following certain vaccinations (e.g., smallpox), and in immune reactions induced by certain drugs (especially phenytoin).**

3-Sinus Histiocytosis:

- is characterized by distention and prominence of the lymphatic sinusoids, owing to a marked hypertrophy of lining endothelial cells and an infiltrate of macrophages (histiocytes).

- Sinus histiocytosis is often encountered in: **Lymph nodes draining cancers** (may represent an immune response to the tumor or its products).

Granulomatous Inflammation

- Large number of diseases that can result in granulomatous formations in lymph nodes. They include;

1. Various types of infections: **Tuberculosis and atypical mycobacteria, Sarcoidosis** (unknown etiology; evidences suggest an infectious cause), **Fungal infections and Cat-scratch disease.**
2. Foreign body reactions.
3. Immunological conditions.
4. Chemical causes; beryllium, zirconium, silica, talc,. Etc.
5. Reaction to malignancy (Lymphoma or metastasis), whether the LN is involved or not by the tumor).

Cat scratch disease

- **A self-limited lymphadenitis caused by the bacterium *Bartonella henselae*.**
- **It is primarily a disease of childhood; 90% of the patients are younger than 18 years of age.**
- **It presents as regional lymphadenopathy, appears approximately 2 weeks after a feline scratch or a splinter or thorn injury, most frequently in the axilla and neck.**
- **A raised, inflammatory nodule or vesicle, is sometimes visible at the site of skin injury.**
- **In most patients the lymph node enlargement regresses over the next 2 to 4 months. Rarely, patients develop encephalitis, thrombocytopenia.., or osteomyelitis.**

CAT SCRATCH DISEASE

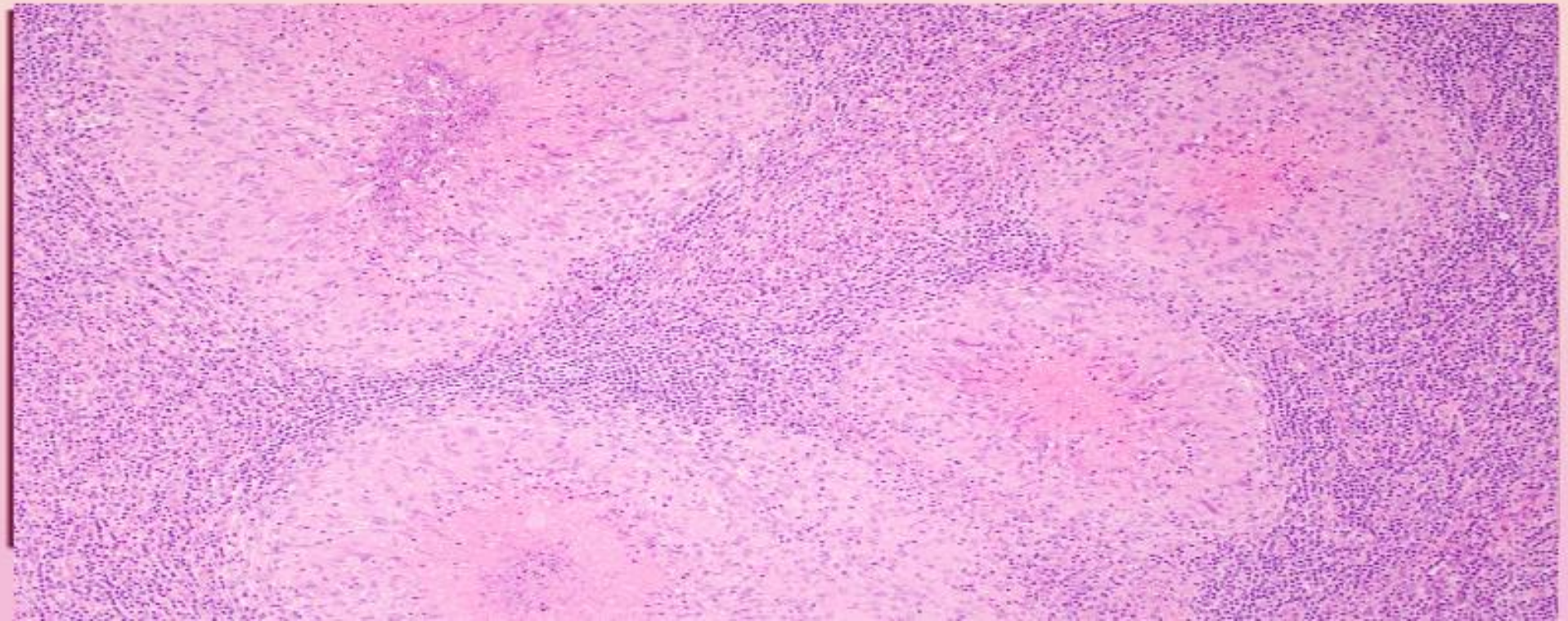
Occurs after cat scratch or flea-bite

Lymphadenopathy -axilla,groin, neck

In children and young adults

Begins as a cutaneous vesicle or papule

Bacterial infection caused by Bartonella henselae



Suppurative granuloma. epithelioid granuloma with Langhans-type giant cell

- *Morphology of Cat scratch disease*

Sarcoid-like granulomas(a form of granulomatous lymphadenitis), these then undergo central necrosis associated with the accumulation of neutrophils forming **irregular stellate necrotizing granulomas** .

- **Diagnosis:**

The diagnosis is based on a history of exposure to cats, the characteristic clinical findings, a positive result on serologic testing for antibodies to *Bartonella,* and the distinctive morphologic changes in the lymph nodes.

Thank you