Lymphoreticular system pathology

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General introduction:

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

1. Myeloid 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. Myeloid leukemia arising in the bone marrow could involve the spleen)

The Lymphoreticular system consists of the tissues of the lymphoid system and the mononuclear phagocyte system (the latter is called also reticuloendothelial system, a terminology used in old literature). The mononuclear phagocyte system includes monocytes, tissue macrophages, the endothelium lining the sinusoids of the spleen, lymph nodes, and bone marrow, and the fibroblastic reticular cells of hematopoietic tissues.

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

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, including the lymph nodes, spleen, and lymphoid tissues of the alimentary and respiratory tracts.

Mucosa-associated lymphoid tissue (MALT): includes

1- discrete lymphoid structures such as in the appendix, 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

The structure of lymph node:

<u>The lymph node is divided into:</u>

1. <u>Cortex</u>: 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
- The secondary follicle has a germinal center surrounded by a mantle zone of small B-lymphocytes.
- Outside the mantle zone, some lymph node germinal centers have a marginal zone composed of B-lymphocytes.

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

3. <u>Medulla.</u> In the center of the lymph node, it is composed of medullary cords and sinuses. Band T lymphocytes, plasma cells, and macrophages occupy the medullary cords.

Classification of white cell disorders:

1. **deficiency:** leukopenias
2. **proliferations:** Leukocytosis, which is either:

- reactive to microbial agents or other antigens 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

Leukocytosis: <u>An increase in the number of white cells in the blood</u>

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 a ***"leukemoid reaction"***, *this occurs in two major situations: viral infections in children and in severe infections with the release of immature WBCs from bone marrow*

Causes of lymphocytosis (reactive and neoplastic)

1. **1. Infections**
   <u>Acute**:**</u> *infectious mononucleosis, rubella, pertussis,* mumps, infectious hepatitis, cytomegalovirus, HIV, herpes simplex or zoster
   <u>Chronic**:**</u> *tuberculosis, toxoplasmosis, brucellosis,* syphilis

2. **Chronic lymphoid leukemia.**
3. **Acute lymphoblastic leukemia**
4. **Non-Hodgkin's lymphoma (some)**

<u>lymphopenia: it is a reduced lymphocyte count</u>

Causes:

1. Severe bone marrow failure.
2. Corticosteroids 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 occurs early in life and is usually asymptomatic, in developed countries occurs at adolescence and is usually symptomatic.

Transmission to a seronegative “kissing cousin” usually involves direct oral contact. The virus initially infects oropharyngeal epithelial cells and then spreads to underlying lymphoid tissue (tonsils and adenoids), mature B cells are infected and 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.

More important in the control of 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: The diagnosis depends on the following findings: **In increasing order of specificity:**

1. Lymphocytosis with the characteristic atypical lymphocytes in the peripheral blood.
2. A positive heterophil 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 isindicated to differentiate from lymphoma

Clinical course and complications: In most patients, mononucleosis resolves within 4 to 6 weeksOccasionally, one or more complications develop:- Perhaps the most common of these is hepatic dysfunction(the virus produces viral hepatitis which might progress into hepatic failure).Other complications involve the nervous system, kidneys, bone marrow, lungs, eyes, heart, andspleen (splenic rupture can occur due to extensive infiltration of the spleen by the atypical lymphocytes producing enlargement and weakening of the capsule).

EBV is a potent transforming virus that plays a role in the pathogenesis of several human malignancies, including several types of B cell lymphoma (if there is impairment of T-cell immunity)

Non-Neoplastic Conditions of lymph node:

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.** A somewhat distinctive form of lymphadenitis that occurs with cat-scratch disease is described separately later.

Localized	Generalized
local infection	***Infection***
• pyogenic infection, e.g. pharyngitis,	• viral, e.g. infectious mononucleosis,
dental abscess, otitis media,	measles, rubella, viral hepatitis, HIV
• viral infection	• bacterial, e.g. syphilis, brucellosis, tuberculosis, *Salmonella,*
• cat scratch fever	• fungal, e.g. histoplasmosis
• lymphogranuloma venereum	• protozoal, e.g. toxoplasmosis
• tuberculosis	***Non-infectious inflammatory diseases***, e.g. sarcoidosis,
Lymphoma	rheumatoid arthritis,
• Hodgkin's lymphoma	SLE,
• non-Hodgkin's lymphoma	other connective tissue diseases,
Carcinoma (secondary)	***Malignant***
	• leukemias, especially CLL, ALL
	• 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: inflamed 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:

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),

-and meshwork of antigen-presenting follicular dendritic cells.

Causes include Rheumatoid arthritis, Toxoplasmosis, and the early stages of HIV infection.

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 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;

A. Various types of infections: **Tuberculosis and atypical mycobacteria, Sarcoidosis** (unknown etiology; evidence suggests an infectious cause). **Fungal infections and Cat-scratch disease**

B. Foreign body reactions

C. Immunological conditions.

D. Chemical causes; beryllium, zirconium, silica, talc, Etc.

E. Reaction to malignancy (Lymphoma or metastasis), whether the LN is involved or not by the tumor).

Cat scratch disease

A **self-limited lymphadenitis is** 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**, and appears approximately 2 weeks after a felinescratch 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

Morphology of Cat scratch disease

S**arcoid-like granulomas**, then undergo central necrosis associated with the accumulation of neutrophils forming **irregular stellate necrotizing granulomas**.