بسم الله الرحمن الرحيم

Pathology

FINAL | Lecture 4

Benign WBCs Disorders

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

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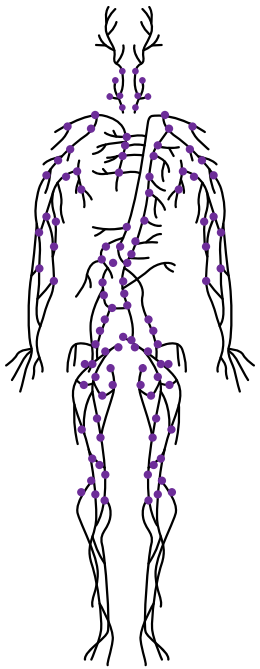

School of Medicine

PATHOLOGY OF HEMATOLYMPHOID SYSTEM
NON-NEOPLASTIC WBC DISORDERS

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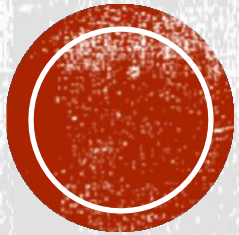


WHITE BLOOD CELL DISORDERS

Those disorders are mostly related to **the number of WBCs**: increased WBCs (leukocytosis), decreased WBCs (leukopenia).

- Disorders include deficiency **(leukopenia)** and proliferation **(leukocytosis).**

- **Leukocytosis:** increased number of WBC in peripheral blood (any cause). Can be benign or malignant, if **benign**, it is called **reactive leukocytosis,** because it happens secondary to a stimulus (as a reaction), but if it was caused by autonomous production from the bone marrow (not a reaction), it's **malignant** and we call it **leukemia**.

- **Leukemia:** increased number of WBC in peripheral blood secondary to **neoplastic** disease.

- Leukocytosis is more **common** than leukopenia [in contrast to RBCs where anemia is more common than polycythemia].

- Reactive leukocytosis is **more** common than leukemia (benign>malignant).

NEUTROPENIA/ AGRANULOCYTOSIS

Another name of neutropenia in clinical practice is agranulocytosis, which is the absence of granulocytes (mainly neutrophils since they constitute the larger portion in peripheral blood). This condition is more serious than neutrophilia which is the increase of number of neutrophils.

- Patients become susceptible to **infections** (namely bacterial and fungal).
- If neutrophil count drops below 500 cells/uL (severe), it leads to **spontaneous infection**, which means getting infected by the normal bacteria in the body.
- It is either caused by:

1. **Decreased production:** previously mentioned in bone marrow deficiencies that lead to pancytopenia (loss of all blood cells): (aplastic anemia, myelophthisic anemia, myelodysplastic syndrome, advanced megaloblastic anemia), chemotherapy which stops the proliferating of all blood cells in the bone and drugs (anti-epileptic, anti-hyperthyroidism)- people administering these drugs should do regular WBC count tests to avoid being susceptible to infections.

2. **Increased destruction:** immune mediated-antibodies against neutrophils (like SLE-Systemic Lupus Erythematosus), anything that causes splenomegaly like hemolytic anemia, because when the spleen enlarges it destructs more neutrophils and platelets, overwhelming bacterial, fungal or rickettsial infections where the microorganisms even destroy neutrophils.

REACTIVE LEUKOCYTOSIS

An increase in any type of white blood cell (WBC) results in an overall rise in the WBC count, known as leukocytosis. Since neutrophils are the most abundant leukocytes in the blood, leukocytosis due to an increase in neutrophils (neutrophilia) is the most common form. In children, however, lymphocytes are more numerous than neutrophils.

Mentioned from most to least common:

1. **Neutrophilia:** infections, inflammation even without the presence of bacteria (necrosis is where dead tissue is present beside inflammatory cells).

2. **Lymphocytosis:** viral infections, Bordetella pertussis infection (bacteria), chronic infections – where lymphocytes become the dominant cells (TB, brucellosis). In children, it is more common than neutrophilia.

3. **Monocytosis:** it's non-specific, can be found in acute and chronic cases, but most commonly in chronic infections: rheumatologic diseases (an autoimmune disease, also elevates lymphocytes), inflammatory bowel disease like Crohn's disease and ulcerative colitis.

4. **Eosinophilia:** it's seen in specific cases only: asthma, allergic diseases, drug sensitivity, parasitic and helminthic infections (worms), and in some types of neoplasms like Hodgkin lymphoma.

5. **Basophilia:** rare, seen in myeloproliferative neoplasms (bone marrow tumors) such as polycythemia Vera.

REACTIVE LYMPHADENITIS

- Again, **reactive** here means it's a **benign** proliferation, secondary to a **stimulus** (a normal reaction to stimulus). **Lymphadenitis** means enlargement of lymph node a result of antigenic stimulation in lymph nodes that cause lymph node enlargement (lymphadenopathy), and since the lymph nodes mainly compose lymphocytes, their proliferation in response to a stimulus is what causes the lymph node enlargement.

- **Lymphadenopathy** refers to the enlargement of the lymph node to the point of it becomes **palpable**, regardless of the cause. Could be benign or malignant.

- It can be **localized** to a certain area in the body like the neck or armpit or **generalized** in the body.

- Enlargement of lymph nodes could be acute or chronic. SEE THE NEXT TWO SLIDES

ACUTE NON-SPECIFIC LYMPHADENITIS

1) **ACUTE NON-SPECIFIC LYMPHADENITIS:** Follows acute infection.

- The patients complain of Swollen, enlarged and painful lymph nodes. The pain occurs because the nerves surrounding the lymph nodes are stretched due to the rapid enlargement. In contrast, chronic lymphadenitis is usually painless, as the lymph node enlargement happens gradually.

- In cases of severe infection, Overlying skin (of lymph node) is red and may develop a **sinus tract** [tract of inflammatory cells connecting the lymph node to the skin due to tissue damage].

- If we take a biopsy and see it under the microscope we notice: The germinal centers in the lymph node are **enlarged** and crowded, infiltrated by **neutrophils** which are not normally present in lymph nodes. With severe infection, **liquefactive necrosis** develops and may enlarge to form an **abscess**.

- In severe cases there are two indications:
  1. **Liquefactive necrosis:** A histological term describing a type of tissue necrosis in which the affected tissue becomes liquefied, there is no shadow of the normal cells and all viable cells are destroyed.

  2. **Abscess formation:** A clinical term referring to a severe localized infection characterized by the formation of a palpable mass due to the accumulation of pus—a mixture of bacteria, dead cells, and inflammatory cells—within a tissue cavity.

CHRONIC NON-SPECIFIC LYMPHADENITIS

2) **CHRONIC NON-SPECIFIC LYMPHADENITIS:** Chronic (benign) enlargement of lymph node, painless (unlike acute). It's associated with three histologic patterns, the first two being the most common:

1. **Follicular hyperplasia:** chronic proliferation of B-lymphocytes, seen in rheumatologic diseases, toxoplasmosis and HIV infection (in HIV, T lymphocytes are affected, so B lymphocytes proliferate instead).

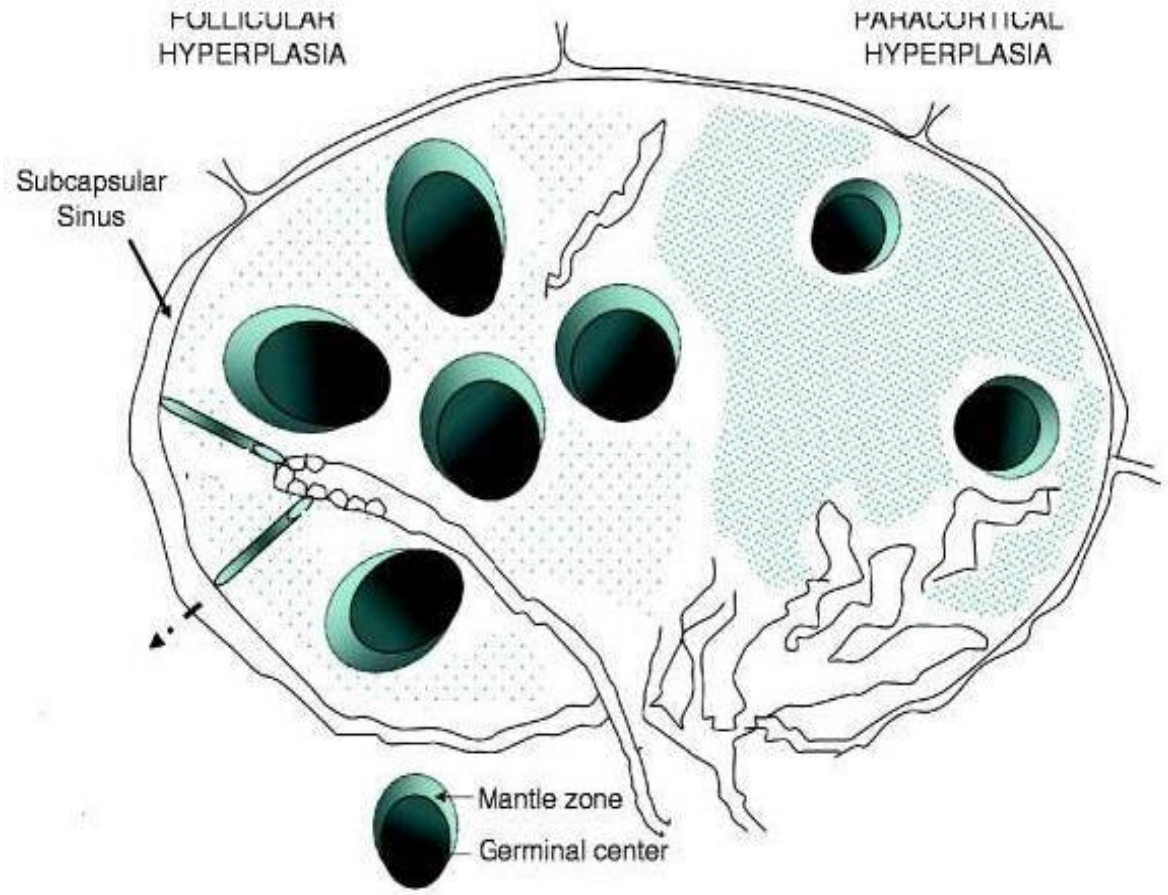
2. **Paracortical hyperplasia:** proliferation of T-lymphocytes, seen in **viral** infections (example EBV), after vaccination and drug reaction (the drug causes eosinophilia when it reacts in peripheral blood, and paracortical hyperplasia when it reacts in lymph nodes).

3. **Sinus histiocytosis:** (the least common) proliferation of macrophages in lymph node sinuses, seen in adjacent cancer.

    - **Histiocytes** are macrophages normally found within the lymph node sinuses. They may proliferate in certain conditions, such as in response to nearby cancers—not due to metastasis within the lymph node itself, but rather due to cancer in adjacent tissues. For example, breast carcinoma can lead to enlargement of the axillary lymph nodes as a result of sinus histiocytosis. Therefore, lymph node enlargement near a tumor site does not always indicate metastasis; it may instead be due to reactive histiocytic proliferation.

CHRONIC NON-SPECIFIC LYMPHADENITIS

- This is a histologic diagram of reactive lymphadenitis. In the picture you can see many lymphoid follicles on the left, they're very large and crowded as well, this indicates **follicular hyperplasia.**
- On the right, however, there's a significant decrease in the number of follicles, and we can see the area between them expanded by T lymphocytes from the paracortex, which indicates **paracortical hyperplasia.**
- On the bottom right of the picture, you can notice **sinus hyperplasia.**



CAT-SCRATCH DISEASE

We will discuss several diseases that can lead to lymph node enlargement. It is important to note that any infection may cause non-specific lymphadenitis, which refers to generalized lymph node enlargement resulting from an immune response to infection.

1) **CAT-SCRATCH DISEASE** (The most important and significant one):

- A bacterial infection caused by **Bartonella henselae** bacteria.
- Transmitted from **cats**, especially young ones (kittens) by either bite, scratch or exposure to infected saliva.
- Most commonly in children and young adults.
- Causes acute **(painful)** lymphadenitis in neck/axilla area (upper part of the body).
- Symptoms appear after two weeks of infection (incubation period).
- In tissue biopsy of lymph node, we will see bacteria causes **liquefactive necrosis** and **necrotizing granulomas** in lymph nodes (remember that granulomas are **non-specific** reactions that can happen in other conditions such as fungal infections and TB).
- Mostly **self-limited** (mild), treated by antibiotics only, and disappeares within a period of 2-4 months, **rarely** can disseminate into visceral organs.

HEHEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH disease)

Hemophagocytic: phagocytosis of RBCs, which causes anemia. Lymphohistiocytosis: increased number of lymphocytes and histiocytes.

2) **HLH** is an uncommon disease, but life threatening.

- Viral infection or other inflammatory agents severely activate macrophages (histiocytes) throughout body to engulf normal blood cells and their precursors in bone marrow.

- Patients have defective genes related to the function of **cytotoxic T cells (CD8+)** and **natural killer cells** (Both of them are the first line cells in killing infected cells by apoptosis), thus they are engaged with their target (virus-infected cells) for a long period (the infected cells take longer time before they're killed) and release excess interferon-γ that activates macrophages.

- Activated macrophages release TNF and IL-6 that causes systemic symptoms of inflammation "fever" (systemic inflammatory response syndrome "SIRS").

HEHEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH disease)

HLH TYPES:

1) **Infants and young children:**

- Homozygous defects in gene PRF1 (perforin1) that encodes perforin which is an essential enzyme in cytotoxic T-lymphocytes and natural killer cells. As its name indicates, this enzyme perforates the cellular membrane of infected cells to kill them, so its deficiency will lead to more engagement with the infected cells thus more activation of macrophages.

2) **Adolescents and adults:**

- X-linked lymphoproliferative disorder (males).
- Defective Signaling lymphocyte activation molecule (SLAM)- associated protein
- Inefficient killing of EBV-infected B-lymphocyte (it only happens in EBV infections).

HEHEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH disease)

3) May be associated with systemic inflammatory disorders:

- (Systemic Inflammation instead of infection) such as rheumatologic diseases (autoimmune).
- Patients have heterozygous genetic defects in genes required for cytotoxic T-cells, but the exact genes are unknown.

4) The fourth type occurs in T-cell lymphomas:

- Malignant T-cells produce aberrant cytokines leading to dysregulation of normal cytotoxic T-cells, again, defects in CD8 cells result in more engagement, more activation of macrophages.
- This type isn't associated with infection.

HEHEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH disease)

HLH SYMPTOMS: usually has rapid symptoms:

1. **Fever:** due to inflammation.
2. **Splenomegaly and hepatomegaly**, because both liver and spleen are infiltrated by activated macrophages.
3. **Pancytopenia:** because macrophages destroy RBCs (remember the name: hemophagocytic) which causes anemia, they also destroy neutrophils (neutropenia), in addition to platelet destruction.
4. **High ferritin:** as an inflammatory marker (acute phase protein).
5. **High triglyceridemia:** most probably because of hepatic dysfunction, which leads to impaired lipid metabolism.
6. **High serum IL-2:** also, an inflammatory marker.
7. **Low level of blood cytotoxic T-cells and natural killer cells:** Although the main problem is in their activity, their levels in peripheral blood will also be low because most of them will be inside tissues.

BM biopsy: numerous macrophages engulfing RBCs, platelets and granulocytes, and that's how it's diagnosed

Pathology Quiz 4

QUIZ

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			