Doctor.021

no. 7

HLS
PATHOLOGY

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WHITE BLOOD CELL DISORDERS

Those disorders are mostly related to the number of WBCs: increased(leukocytosis), decreased (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,** which is the topic of the following lectures.

♣ **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 :(**aplastic anemia, myelophthisic anemia, myelodysplastic syndrome, advanced megaloblastic anemia**), **chemotherapy** which stops the proliferating of all blood cells in the bone marrow**, 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** (like SLE), 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

*Remember, it's a benign condition.

*An increase of any of the types of WBCs causes an increase in WBC count as a whole (leukocytosis). And since the neutrophils are the most abundant leukocytes in peripheral blood, leukocytosis caused by the increase of number of neutrophils (neutrophilia) is the most common, followed by leukocytosis that is caused by the increase in the number of the second most abundant WBC (lymphocyte), which is called lymphocytosis, and so on.

*In children the amount of lymphocytes is more than neutrophils

*Mentioned from most to least common:

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

♣ **Lymphocytosis: viral infections, Bordetella pertussis infection** (bacteria), **chronic infections (TB, brucellosis)**

♣ **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.

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

♣ **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 a stimulus). And lymphadenitis simply means enlargement of lymph node. So, this disease is a result of **antigenic stimulation in lymph nodes** that **causes lymph node enlargement (lymphadenopathy),** and since the lymph nodes mainly composes of

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 it becomes palpable, regardless of the cause. Could be benign or malignant.

♣ **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:

1) ACUTE NON-SPECIFIC LYMPHADENITIS

Follows acute infection.

♣ **Swollen, enlarged and painful lymph nodes** (the nerves surrounding the lymph nodes stretch and cause pain because of the rapid enlargement of the lymph node, unlike chronic lymphadenitis which is painless because the enlargement is gradual)

♣ **Overlying skin** (of lymph node) **is red and may develop a sinus tract**: a 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, 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 histologic term referring to the presence of necrosis in tissue, it becomes liquid and all the viable cells are destroyed.
2- Abscess formation: a medical term that refers to a tissue mass that contains bacteria + dead cells + inflammatory cells.

2) CHRONIC NON-SPECIFIC LYMPHADENITIS

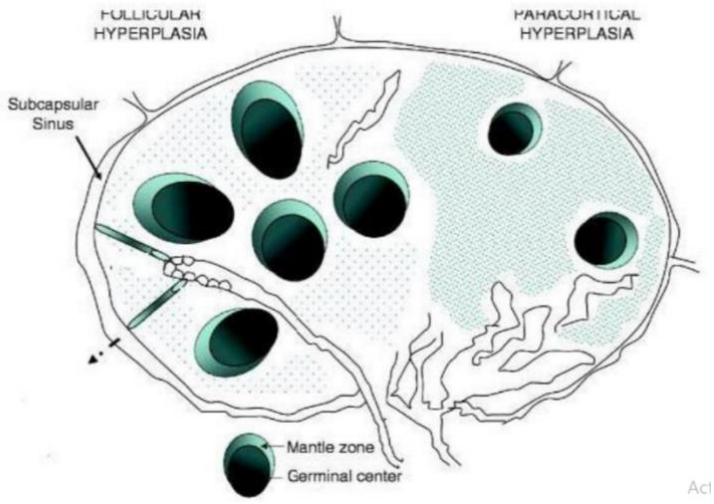
♣ **Chronic** (progressive) **enlargement of lymph node, painless** (unlike acute)

*It's associated with three histologic patterns, the first two being the most common and most important:

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 (so 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 that are normally localized in lymph node sinuses. They proliferate in certain cases like cancers, but not by cancer in the lymph node itself, rather cancer in adjacent tissues, such as breast carcinoma that causes enlargement of the axillary lymph nodes due to histiocytosis. Thus, the enlargement of lymph nodes near the site of cancer does not necessarily indicate metastasis, as it could simply be caused by sinus histiocytosis.



- In the picture you can see many lymphoid follicles on the left, they're very big 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.
- and on the bottom right of the picture, you can notice sinus histiocytosis.

Any infection can cause non-specific lymphadenitis (lymph node enlargement), but we will talk about the most important and significant one:

CAT-SCRATCH DISEASE

- ♣ A bacterial infection caused by **Bartonella henselae** bacteria
- ♣ **Transmitted from cats** especially young ones (kittens) by either **bite or scratch** or exposure to **infected saliva**
- ♣ **Most commonly in children** and young adults
- ♣ **Causes acute** (meaning it's painful) **lymphadenitis in neck/axilla area** (upper body)
- ♣ **Symptoms appear after two weeks of infection** (incubation period)

In tissue biopsy of lymph node we 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** (treated by antibiotics only) **in 2-4 months, rarely can disseminate into visceral organs**

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Let's analyze the name:

Hemophagocytic: phagocytosis of RBCs, which causes anemia.

Lymphohistiocytosis: increased number of lymphocytes and histiocytes.

- ♣ **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** (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 (systemic inflammatory response syndrome "SIRS")**

HLH TYPES

1) **Infants and young children**

♣ **Homozygous defects in gene PRF1** (perforin1) **that encodes perforin** which is **an essential enzyme in** (secreted by) **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 thus more activation of macrophages.

2) **Adolescents and adults**

♣ **X-linked lymphoproliferative disorder (males)**

♣ **Defective Signaling lymphocyte activation molecule (SLAM)-associated protein**

*the underlined words give us a clue of EBV infection, as it affects lymphocytes.

♣ **Inefficient killing of EBV-infected B-lymphocyte** (it only happens in EBV infections).

3) **May be associated with systemic inflammatory disorders** (not 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.

HLH SYMPTOMS:

HLH usually has rapid symptoms:

♣ **Fever:** due to inflammation.

♣ **splenomegaly** and hepatomegaly, because both liver and spleen are infiltrated by macrophages.

♣ **pancytopenia:** because macrophages destroy RBCs (remember the name: hemophagocytic) which causes anemia, they also destroy neutrophils (neutropenia), in addition to platelet destruction.

♣ **High ferritin:** as an inflammatory marker (acute phase protein)

♣ **High triglyceridemia:** most probably because of hepatic dysfunction, which leads to impaired lipid metabolism.

♣ **High serum IL-2:** also an inflammatory marker.

♣ **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.

BEST OF LUCK