Sheet No. 6

# PATHOLOGY


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# Today, we are going to discuss the diseases of white blood cells and begin with the benign ones.

## Numeric abnormalities

- When the number of **WBC is below normal**, we call it **leukopenia**.
- When there is an **increased proliferation**, we call it **leukocytosis**.
- **Benign leukocytosis** is called **reactive leukocytosis** while the **malignant leukocytosis** is called **leukemia**.
- Leukemia: increased number of WBC in peripheral blood due to neoplastic diseases
- Leukocytosis is **much more common** than leukopenia → In contrast, to the RBC disorders where anemia was more common than polycythemia.
- Reactive leukocytosis is **more common** than leukemia
- When the number of **granulocytes** {basophils, eosinophils and neutrophils} is **below normal**, we call it **agranulocytosis**. The most affected cell is the neutrophil, and this reduction in the number of neutrophils is called **neutropenia**.
- These Patients become susceptible to infections, most importantly bacterial and fungal.
- Neutrophil is the most common WBC in the blood, and in pathology we care about what is called the absolute neutrophil count. We calculate it by:

  The percentage of neutrophils **X** the total WBC count

- The absolute neutrophil count is generally **above 1200-1500 cells/uL**.
- If neutrophil count drops below this, then the patient has neutropenia
- The lower the absolute neutrophil count is, the more severe the situation is.
- If neutrophil count drops **below 500 cells/uL,** this is a **severe form of neutropenia** and the patient becomes very susceptible to infection. They can have a **spontaneous infection** by the normal flora or by any bypassing bacteria.
- Neutropenia could be due to (1) **decreased production** or (2) **increased destruction**.

Neutropenia

**Decreased production**

- aplastic anemia
- myelophthisic anemia
- myelodysplastic syndrome
- paroxysmal nocturnal hemoglobinuria
- advanced megaloblastic anemia
- chemotherapy (suppress the bone marrow)
- drugs (anti-epileptic, anti-hyperthyroidism) suppress a single line in the BM (only granulocytes).

**Increased destruction**

- Immune mediated (autoimmune)
- severe cases of splenomegaly ->The spleen destroys the neutrophils alongside RBCs.
- Overwhelming bacterial infection (overcomes the immune system).
- some bacterial types like rickettsia are common to cause more neutropenia.
- fungal infections.

Let's go back to Reactive Leukocytosis, **the benign increased proliferation in WBCs**.

## Reactive Leukocytosis

- ♣ Very common (most of humans have developed it at some time of their life)
- ♣ Has many forms:

| | |
|---|---|
| Neutrophilia | **Where the most predominant cell is the neutrophil, MOST COMMON,** common in **infection** (with liquefactive necrosis) and **inflammation**, like in coagulative necrosis (results from ischemia) |
| Lymphocytosis | Common in **viral** infections and **chronic** infections (TB, brucellosis). An exception of a bacterial strain that causes lymphocytosis is **Bordetella pertussis**. |
| Monocytosis | Monocytes increase in **both acute and chronic** infection but in the **chronic** infection, they become more **predominant,** in rheumatologic diseases (again chronic diseases), and in inflammatory bowel diseases (chronic inflammation in the gut). |
| Eosinophilia | Eosinophils become predominant in **asthma**, **allergic diseases** (in general, either in the skin or the systemic ones), **drug hyper-sensitivity**, **parasitic infections** (+ helminths) and in some **neoplasms**, the most famous one is **Hodgkin Lymphoma**. |
| Basophilia | This is a **rare** situation, and is usually **neoplastic**. It appears in myeloproliferative neoplasms. |

→ Now, the home of the lymphocytes is the lymph nodes. If we have an **antigenic stimulus** in the LN, it will cause **enlargement,** and this is called **reactive lymphadenitis**.

## Reactive Lymphadenitis

- ♣ **Benign** (non-neoplastic), **inflammation** of the Lymph Nodes.
- ♣ Clinically, these patients will have **lymphadenopathy**. This is because an antigen stimulus causes proliferation of lymphocytes, so the **LN is enlarged**.
- ♣ It can be **localized** in certain areas like in the neck **or generalized** in the entire body according to the type of stimulus.

### A. Acute Non-Specific Lymphadenitis

- ♣ A very **common** situation
- ♣ The patient has **acute inflammation** secondary to either **bacteria or a virus**
- ♣ It causes **swollen**, large and **painful** lymph nodes
- ♣ The swelling is really fast so it stretches the nerves and becomes painful

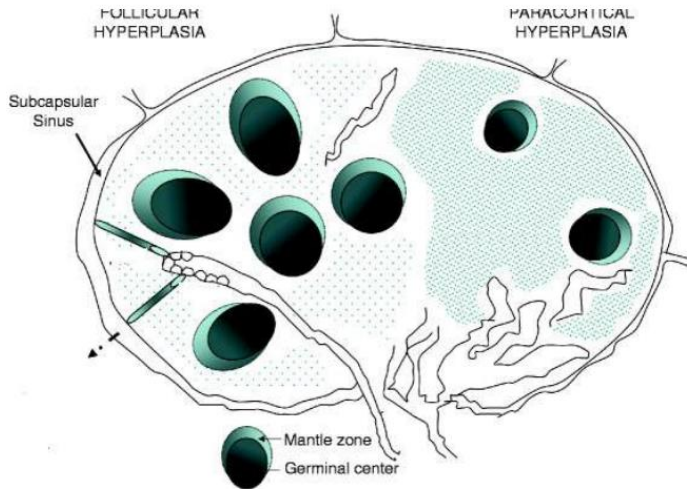
- ♣ Sometimes, especially in **bacterial infections**, and if the inflammation is **severe**, it will damage the more **superficial** structures of the body and it can reach the skin.
- ♣ So, the **skin** becomes **erythematous (red)** and may develop a **sinus tract** (there is a destruction of an entire tract from the lymph node to the skin, so we can see pus coming out in that area).
- ♣ Under the microscope, the germinal centers in the lymph node are **enlarged** (because they are stimulated), infiltrated by **neutrophils** (like in bacterial infections).
- ♣ With **severe** infection, **liquefactive necrosis** (infection) develops and may enlarge to form an **abscess** (can be seen by the naked eye).
  10:30

## B. Chronic Non-Specific Lymphadenitis

- ♣ Chronic enlargement of lymph node, painless
- ♣ **Follicular hyperplasia**: **numerous follicles but they are benign**, chronic proliferation of B-lymphocytes, seen in rheumatologic diseases, toxoplasmosis and HIV infection (HIV also destroy helper Tcells).
- ♣ **Paracortical hyperplasia**: diffuse area which looks like a solid sheet (no specific pattern) and follicles become less in number, proliferation of **T-lymphocytes**, seen in **viral** infections (For example **EBV**), after vaccination and **drug reaction** (not a specific category) →
- ♣ **Sinus histiocytosis**: **LEAST COMMON**, proliferation of **macrophages** in lymph node sinuses, this is prominent in patients with **adjacent cancer** (most commonly in the axillary LN, next to breast cancer).

**Recall** many drugs have different reactions in the body. it could cause:

- Agranulocytosis (neutropenia)
- Eosinophilia
- Paracortical Hyperplasia



## Cat-Scratch Disease

- *Bartonella henselae*
- Transmitted from cats (bite, scratch, infected saliva)
- Most commonly in children
- Causes acute lymphadenitis in neck/axilla area
- Symptoms appear after two weeks of infection
- Bacteria causes liquefactive necrosis and necrotizing granulomas in lymph nodes
- Mostly self-limited in 2-4 months, rarely can disseminate into visceral organs

## Hemophagocytic Lymphohistiocytosis (HLH)

- HLH is an uncommon disease **(rare)**
- It is a critical disease as patients could die if they are not diagnosed and didn't receive the appropriate therapy.
- Most commonly, it follows a **viral infection** or other inflammatory agents
- The hallmark of HLH is **severe activation of macrophages** (histiocytes) throughout the body to engulf normal blood cells and their precursors in bone marrow.
- Usually, patients have **defective genes** related to the function of **cytotoxic T cells** and **natural killer cells** (the defective genes code for defective enzymes), thus they are engaged with their target (virus-infected cells) for a **long period** and **release excess interferon-γ that activates macrophages**.
- Activated macrophages release **TNF** and **IL-6** that causes systemic, **severe symptoms of inflammation** (systemic inflammatory response syndrome "SIRS")

– Simple viral infection will result in severe activation of macrophages

| Types of HLH | |
|---|---|
| **Type 1** | **Type 2** |
| ♥ **Infants** and **young** children<br>♥ **Homozygous defects** in gene PRF1 that encodes **perforin**.<br>♥ An **essential enzyme** in cytotoxic T-lymphocytes and natural killer cells | ♥ **Adolescents** and **adults**<br>♥ **X-linked lymphoproliferative disorder (males)**<br>♥ Most of us have been infected with EBV but we develop immunity.<br>♥ Very rarely, some males, with X-linked problems in their genes, cannot fight this infection.<br>♥ The problem here is a **defective enzyme** called Signaling lymphocyte activation molecule **(SLAM)-associated protein**<br>♥ So, the Cytotoxic T Cells are inefficient in the killing of EBV-infected B-lymphocytes.<br>♥ EBV infection --> Proliferation of B cells--> T cells cannot counter them--> severe activation of macrophages. |

| Types of HLH | |
|---|---|
| **Type 3** | **Type 4** |
| ♥ May be associated not with infection but with **systemic inflammatory disorders** such as rheumatologic diseases (arthritis)<br>♥ Patients have **heterozygous genetic defects in genes required for cytotoxic T-cells**<br>♥ Not a certain gene because there are many ones. | ♥ **T-cell lymphomas**<br>♥ **Malignant** T-cells produce **abnormal cytokines** leading to dysregulation of normal cytotoxic T-cells so they cannot kill the infected cell. |

NOTE: they all share the same common pathway at the end.

## *SYMPTOMS OF HLH*

Symptoms of Severe Systemic Inflammation.

- ♣ **Fever**, **splenomegaly** (spleen full of macrophages) and **pancytopenia** (see last point)
- ♣ High **ferritin**
- ♣ High **triglyceridemia** (increases acute phase proteins which are inflammation markers)
- ♣ High serum **IL-2**
- ♣ **Low level** of blood **cytotoxic T-cells** and **natural killer cells** → peripheral
- ♣ BM: numerous macrophages engulfing RBCs, platelets and granulocytes

GOOD LUCK ☺