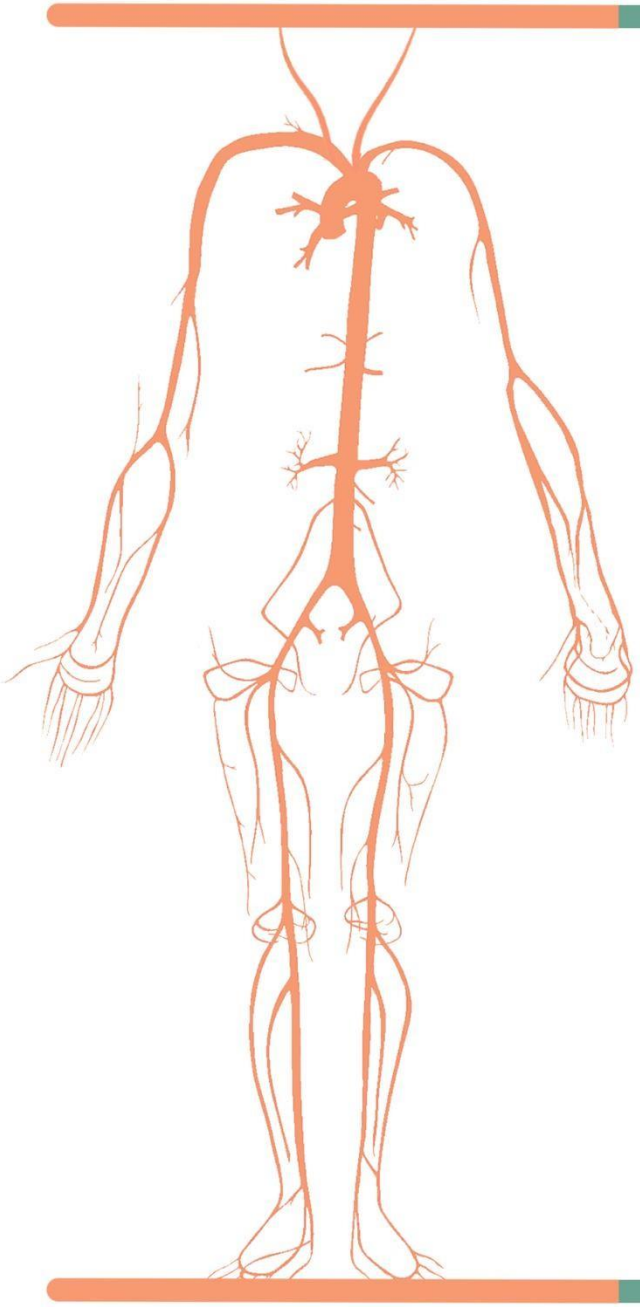
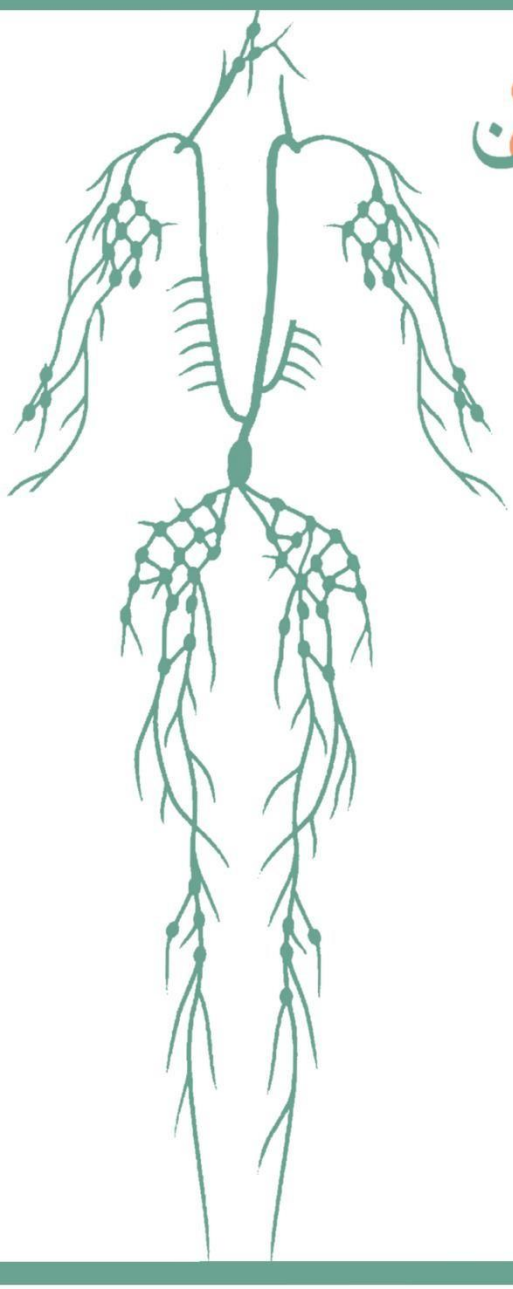
Pathology

HematoLymphatic





Title: Sheet 10 - MPN and LCH

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Today's topic is about:

1. **Myeloproliferative Neoplasms**
   - ♣Chronic Myeloid Leukemia
   - ♣Polycythemia Vera
   - ♣Primary Myelofibrosis
   - ♣Essential Thrombocytopenia
2. **Langerhans Cell Histiocytosis**
   - ♥Multisystemic LCH
   - ♥Unisystem LCH

So, Let's begin :)

Myeloproliferative Neoplasms (MPN)

♣**Normal Maturation**(cells appear normal in morphology) but **Proliferation is high** (present in a very large amount).

♣Generally, we have a permanently **active tyrosine kinase pathway** (so the cells keep on proliferating) and they are **independent of the normal growth factors/hormones** (they don't need them as they keep on dividing).

♣As a result, we end up with a **hypercellular BM** and increased number of cells (**cytosis**) in the peripheral blood (leukocytosis, thrombocytosis, and erythrocytosis) ⟶

Remember! we have **cytopenia** in Myelodysplastic syndromes **(MDS)**

♣**VERY COMMON FINDING**--> The Neoplastic stem cells in MPN **go outside the BM** and often seed to the spleen, liver and sometimes LNs, thus they give rise to **extramedullary hematopoiesis**. So, the patient will end up with **hepatosplenomegaly**.

♣They have the **tendency to transform into Acute Myeloid Leukemia (AML)** with time because they gain more mutations.

♣We are going to discuss 4 subtypes of MPN:

A. Chronic Myeloid Leukemia (CML)

This a counter to Chronic Lymphoid Leukemia (CLL)

♣**MOST COMMON MPN**

♣Chronic → clinically AND on cell level the cells will appear mature in the morphology (NOT blasts).

♣**Harbor t(9;22)**--> Philadelphia chromosome (the name of this reciprocal translocation), and at the genetic level, this results in **fusion of Bcr/Abl genes** and so they produce a **new tyrosine kinase** that keeps the cell dividing with a **prolonged cell survival**.

This translocation also occurs in B acute lymphoblastic Leukemia (BALL), in adults

♣This mutation is present in **ALL CML patients** and in some BALL patients

♣This mutation is present in all BM cells, specifically the stem cells (myeloid, erythroid, megakaryocytes, and even sometimes in the lymphoid cells).

♣All of these cells increase in number but what is the **MOST PROMINENT** cell in proliferation? →**MYELOID CELLS**.

♣Affects **young and old** adults (25-60 years).

♣***Symptoms***→ generally **non-specific**→ fatigue, heavy abdomen (due to splenomegaly) and weight loss.

♣***Treatment***→ **Imatinib** → tyrosine kinase inhibitor and specific for **Bcr/Abl mutation** (targeted therapy).

♣CML starts as a chronic disease but with time (with or without the usage of the Imatinib), the patients go into an **ACCELERATED PHASE**→ worsening of symptoms, higher WBC count, development of thrombocytopenia (instead of thrombocytosis), and sometimes even resistance to Imatinib.

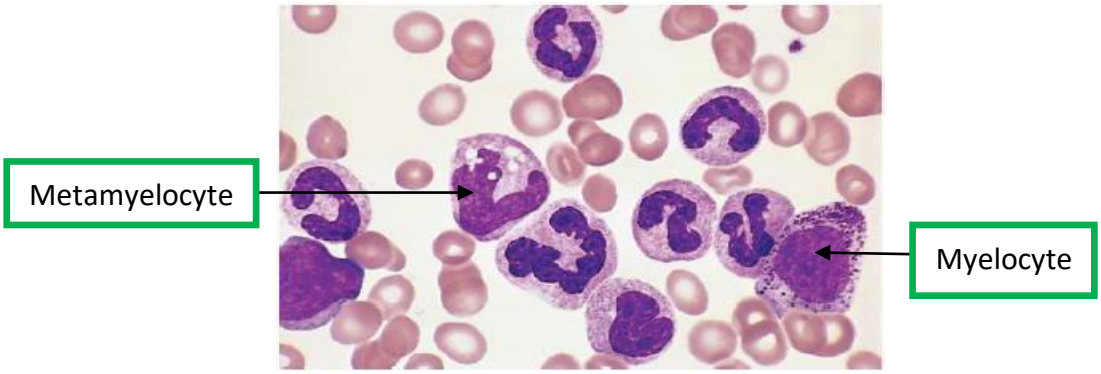
♣After that phase, there is a **BLAST PHASE/CRISIS**→ transformation to acute myeloid leukemia (**AML**) or sometimes even acute lymphoblastic anemia (**ALL**) as this mutation can also involve a lymphoid tissue(AML>ALL).

♣The Blast crisis is when **they reach 20%** of the BM cells or the peripheral blood cells.

♣The Blast crisis **doesn't have to follow this order** (Chronic → Accelerated → Blast). It can occur suddenly in the course of Chronic disease without the Accelerated phase.

♣***Morphology***:

- ⇨**Leukocytosis** (high number of mature WBCs and a lot of them are **Neutrophils**), can be >100K (**High Count)**
- ⇨Also, **Basophilia** and **eosinophilia**
- ⇨**Shift to left** → presence of the **precursor cells** of the myeloid cells (**NOT blasts**) in the peripheral blood, like myelocyte and metamyelocyte.
- ⇨**Thrombocytosis** is common (Megakaryocytes also carry this mutation).
- ⇨**Iron deficiency anemia** (instead of erythrocytosis), as those WBCs take the iron from the BM.
- ⇨**BM** biopsy → increased myeloid and megakaryocytes (**hypercellular**).
- ⇨**Spleen** → Extramedullary Hematopoiesis (**EMH**).
- ⇨**Blasts** count →**low** (below 20%).
- ⇨**Leukemoid reaction** (looks like leukemia)→it's a benign condition where there is **high WBC** count and **shift to left**. It occurs in **severe inflammation** like in **sepsis** or **severe trauma**. *It could also occur in CML, but how can we differentiate it ?* In CML, we have basophilia, eosinophilia, and thrombocytosis. Also, we can test for the Bcr/Abl gene mutation. The leukemoid reaction is benign and **reversible** so if we stop the inciting factor (like inflammation), the symptom will go away by itself.



B. Polycythemia Vera

♣Mutation in **tyrosine kinase JAK2**

♣JAK2 normally acts in the signaling pathway of **erythropoietin receptor** and other **growth factor receptors.**

♣So, when it is mutated, its function is kept active and the hematopoietic cells become **less dependent** on growth factors and erythropoietin.

♣**HALLMARK OF THE DISEASE**: **Excessive proliferation of erythroid cells.**

♣There is also proliferation of megakaryocytes and myeloid cells.

♣This is the **ONLY** disease in which we have proliferation in erythroid **AND** it results in **panmyelosis**. →

Panmyelosis: neoplastic proliferation and maturation of erythroid, megakaryotic and granulocytic elements.

♣In the peripheral blood, **erythrocytosis** is most prominent and results in **polycythemia** (increased Hb concentration), and we have **low erythropoietin level** (negative feedback).

♣**Remember!** we differentiate polycythemia vera from secondary or reactive polycythemia by the erythropoietin level. The secondary polycythemia has high erythropoietin level.

♣**Clinically**, we have **chronic** and insidious onset of symptoms.

♣Patients are usually →**middle age**, **plethora**(skin full of erythema) and sometimes **cyanosis** (deoxygenated Hb) so the skin could be red or blue, **headache**, **dizziness** (due to hypertension as result of increased blood mass), **pruritis** (having the urge to itch the skin especially after the shower and this is secondary to activation of basophils), and **peptic ulcer** (due to the secretion of histamines from the basophils). 10:40

♣**More Serious Symptoms** ---> **Thrombosis** (high number of RBCs can make a thrombus, causing the circulation to be slow and very viscous) which is fatal as it can lead to **tissue infarction**. On the other hand, **bleeding** is also common in the **GIT** as we have increased number of platelets, but they have impaired function. Some patients develop **gout** (precipitation of uric acid due to the large production of hematopoietic cells and this leads to gout/arthritis).

♣Patients stay in the **chronic phase** for a long period of time. After that, we have the **Spent phase**→ occurs after an interval of **10 years** of symptoms, **BM** becomes **fibrotic** so the hematopoiesis shifts to spleen→**MORE splenomegaly**.

♣It can be followed by **Blast crisis**: transformation to AML (but it is **very rare** unlike CML).

♣**Treatment**→**phlebotomy** (blood draw), and recently we have **JAK2 inhibitor** that blocks the function of the permanently active protein.

♣**Laboratory Findings:**

⇨**High RBC** count (erythrocytosis)

⇨**Hematocrit** →above 60%

⇨**Hemoglobin** → above 18 g/dl for Males and above 16 g/dl for Females (polycythemia)

⇨**Leukocytosis** is common, including Basophilia

⇨**Thrombocytosis** is common

Polycythemia --->Thrombosis

Thrombocytosis --->Bleeding

C. Primary Myelofibrosis

♣**Primary**→ the problem is in the BM itself.

♣In addition to Myeloproliferative neoplasm, we have **Overt BM fibrosis** (severe fibrosis in the BM), **reducing capacity for hematopoiesis.**

♣So, it begins with **hypercellular BM** then **hypocellular but it's fibrotic** (dense fibrosis displacing the Fat in the BM).

♣This eventually leads to **cytopenia** (after cytosis) and massive **extramedullary hematopoiesis** in the spleen (EMH).

♣***Mutation***→ **JAK-STAT signaling pathway** is active in all cases.

♣**50%** have mutation in **JAK2** while **5%** have mutation in **MPL gene** (thrombopoietin receptor).

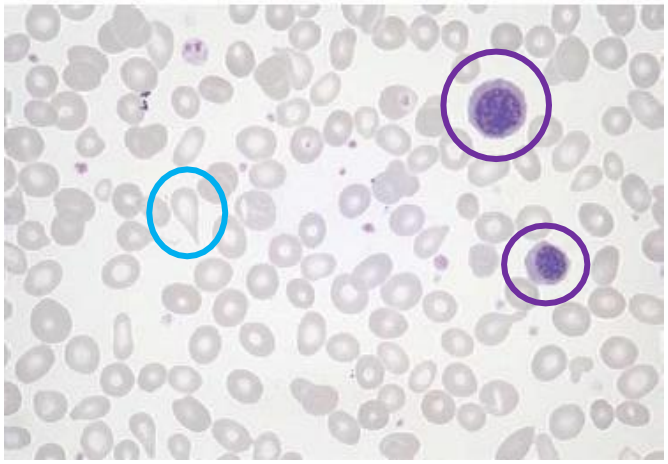
♣All of them share **the same signaling pathway**. The rest of the cases have a problem in the **JAK-STAT** signaling pathway, but we still don't exactly know which genes are causing them.

♣**HALLMARK OF THIS DISEASE**→**FIBROSIS**. This is because **neoplastic megakaryocytes** secrete a large amount of **TGF-B**, which activates **fibroblasts** in BM to deposit **reticulin** and **collagen** fibers which efface and **remove hematopoiesis** and **Fat cells.**

♣It also causes **ANGIOGENESIS**→ Large vascular spaces in the BM.

♣Another characteristic →**RBC production is very impaired**→ patients always have **anemia**. Also, the RBCs have a special shape characteristic called **tear-drop.**

♣The **reason** for the development of the tear-drop is **not quite known**. Sometimes, it is secondary to the **fibrosis** where the RBC becomes distorted when it exits the BM. Sometimes, it is related to the **spleen** because it also produces hematopoiesis, but this doesn't explain why it only develops in this disease.



♣**Morphology:**

⇨Peripheral blood → **tear-drop cells**, **nucleated RBCs**, **shift to left** → together, we call it **leucoerythroblastic anemia which is characteristic of myelofibrosis**.

⇨**WBC** → can be normal OR increased

⇨**Platelets** → High, but with time it becomes low due to fibrosis.

⇨**BM** → (1) **EARLY**: hypercellular (MPN) and focal fibrosis (2) **LATE**: hypocellular and extensive fibrosis.

⇨**DOMINENT CELLS**→**Megakaryocytes**→ they are increased and will form clusters → these cells are individual cells but when they form clusters, this is abnormal and a sign of myelofibrosis.

♣**Clinical Features:**

⇨**WORST TYPE OF MPN :(**

⇨**Non-specific symptoms**→ **weight loss**, **anemia**, **massive splenomegaly** (This is **really bad** as it is very large and can reach the other side of the abdomen, so anatomically it crosses the midline of the abdomen. This results in a heavy abdomen and discomfort), **gout**, **bleeding** (platelets are high but still it can cause bleeding) and/or **infection**.

⇨Worse outcome than CML and P Vera. 4-5 years survival

⇨Frequent transformation to AML (5-20%) → like CML or even higher

♣**Treatment:**

⇨**JAK2 inhibitor** → it causes a decrease in splenomegaly and relief of symptoms.

D. Essential Thrombocythemia

♣Cythemia→ Cytosis

♣Best outcome and **mildest** disease :)

♣Predominantly →**THROMBOCYTOSIS**, and occasionally **leukocytosis**

♣**JAK2 mutation** is sometimes positive, but **NO bone marrow fibrosis**

♣It is similar to myelofibrosis in having thrombocytosis and JAK2 mutation BUT we do **not** have **BM fibrosis** and we do **not** have **leucoerythroblastic anemia**.

♣**Splenomegaly** is positive in only **50%**

♣**Good outcome**

20:29

Now, we are done with the Myeloid Neoplasms, and the last disease we will talk about is a type of neoplasm that affects the Langerhans and Histiocytic cell lines called Langerhans Cell Histiocytosis.

Langerhans Cell Histiocytosis (LCH)

- ♥The histiocyte (macrophage) is somehow different from the Langerhans dendritic cell but in this disease, the term is mixed.
- ♥**Neoplasm of dendritic cells.**
- ♥**Dendritic cells** are **antigen-presenting cells** that look like a spindle (thin) and have cytoplasmic projections (dendrites) to capture the antigens and present them **to lymphocytes and histiocytes**.
- ♥Now, Langerhans cells express 2 markers →**CD1a** and **Langerin.**
- ♥**Langerin** is a transmembrane protein, attached to **Birbeck granules** in the cytoplasm (these granules have a **tennis racket shape** and the best way to view them is under electron microscope).
- ♥In this disease, the **proliferating Langerhans cells differ in shape** →they become **large** and **vacuolated**→similar to macrophages (round and large) →hence, the name histiocytosis.
- ♥**PATHOGENESIS (IMPORTANT)**---> recently, it was discovered that it has a **mutation** in **serine/threonine kinase BRAF**, which leads to hyperactivity of this kinase, inducing proliferation of the dendritic cells.
- ♥**Remember!** we discussed this kinase mutation in **Hairy Cell Leukemia,**and it is common in **solid tumors** as well as **melanoma**.
- ♥**Langerhans Cell Histiocytosis** is a **solid tumor** and it develops in tissues, so it is **not a leukemia**.
- ♥There are 2 major categories of LCH:

A. Multisystemic LCH

- ♥ Multisystemic ---> the patient has a disease in multipleorgans.
- ♥ Occurs **mostly in children** (less than 2years).
- ♥ **Multiple skin (cutaneous) lesions** as masses (tumors) → they are composed of Langerhans Cells.
- ♥ **Hepatosplenomegaly** and **lymphadenopathy.**
- ♥ **Pulmonary lesions** are common → bad symptoms:(
- ♥ **Osteolytic** lesions → these cells **proliferate in the bone in numerous areas**, similar to plasma cell myeloma but in plasma cell myeloma, they are functional neoplastic cells which cause bone erosion while the multisystemic LCH only causes **physical destruction to the BM** (reabsorption and destruction).
- ♥ **Extensive bone marrow infiltration** which leads to **myelophthisic anemia** and **pancytopenia.**
- ♥ **Treated with chemotherapy.**
- ♥ Survival is around 5years.

B. Unisystem LCH

♥**Eosinophilic granuloma** is a more common name for this disease.

♥This disease is **heterogeneous**→ it comes in a single organ but with different medical conditions.

♥It affects the **bone** (**MOST COMMONLY and usually in children**), then **skin**, **lung** (in **old adults** and usually **smokers**), and **stomach.**

♥Can be **unifocal** or **multifocal** but within the same organ.

♥**Unifocal** is commonly **asymptomatic** (we do an x-ray for a child and we see a small osteolytic lesion in the bone) and sometimes it can cause **pain.**

♥**Multifocal** unisystem disease presents in **children**, commonly affects the **skull bone** (calvaria bone), and sometimes it **extends outside the bone** and it affects the **pituitary gland**. This results in **diabetes insipidus** (patients will urinate like they have diabetes) and also, due to neural damage, it will result in **exophthalmos.**

♥This triad :(1) osteolytic lesion (2) diabetes insipidus (3) exophthalmos is called **Hand-Schuller-Christian triad**. This is a **rare** situation.

♥Under the microscope, **proliferating LCs** are **admixed** with other numerous cells like **EOSINOPHILS** (hence, the name eosinophilic granuloma), **lymphocytes**, **plasma cells,** and **neutrophils**. This reminds us of Hodgkin Lymphoma, but in the HL there are a few cancerous cells, while in the eosinophilic granuloma there are numerous cancerous cells.

♥**Treatment:**

⇨**UNIFOCAL→surgical excision**

⇨**MULTIFOCAL →chemotherapy**, and this disease is known to have a **spontaneous regression,** and this is a rare phenomenon in cancer. It could regress on its own and it could be related to the activation of the immune system that removes this tumor.

GOOD LUCK