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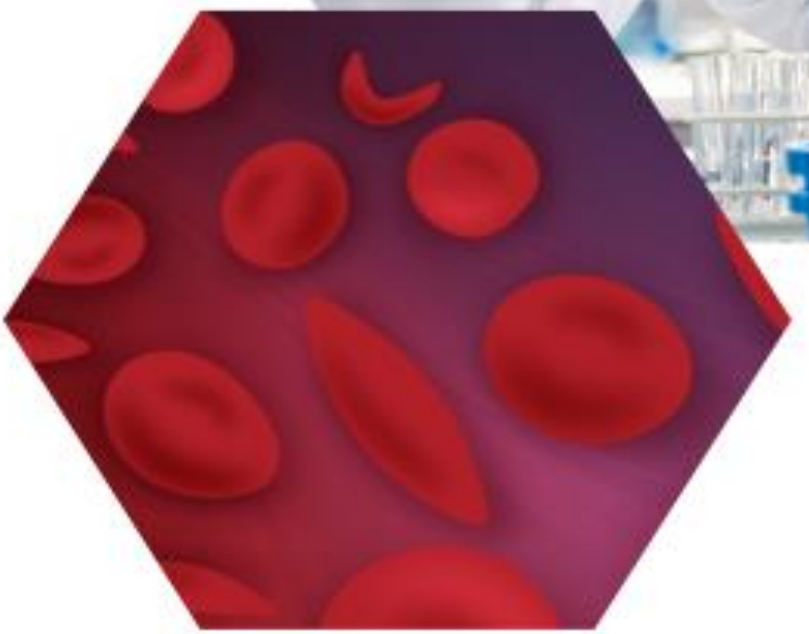
HLS PATHOLOGY



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Doctor:

Today's topic is about:

1. **Myeloproliferative Neoplasms**
   - Chronic Myeloid Leukemia
   - Primary Myelofibrosis
   - Essential Thrombocytopenia
2. **Myelodysplastic syndrome**

So, Let's begin :)

Myeloproliferative Neoplasms (MPN) (group of diseases, BM cells transformed into neoplastic)

- **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)**

Note: normal BM with aging the fat content increased

- **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**.
  - Tendency to develop a "**spent phase**" after along time, characterized by bone marrow fibrosis
- They have the **tendency to transform into Acute Myeloid Leukemia (AML)** with time because they gain more mutations.
- We are going to discuss 3 subtypes of MPN: (the 4th is polycythemia vera)

A. Chronic Myeloid Leukemia (CML)

- **MOST COMMON MPN**

Peak incidence is 4th – 5th decade

- 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 mutation is present in **ALL CML patients**
- This mutation is present in all BM cells, specifically the stem cells (myeloid, erythroid, megakaryocytes)

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

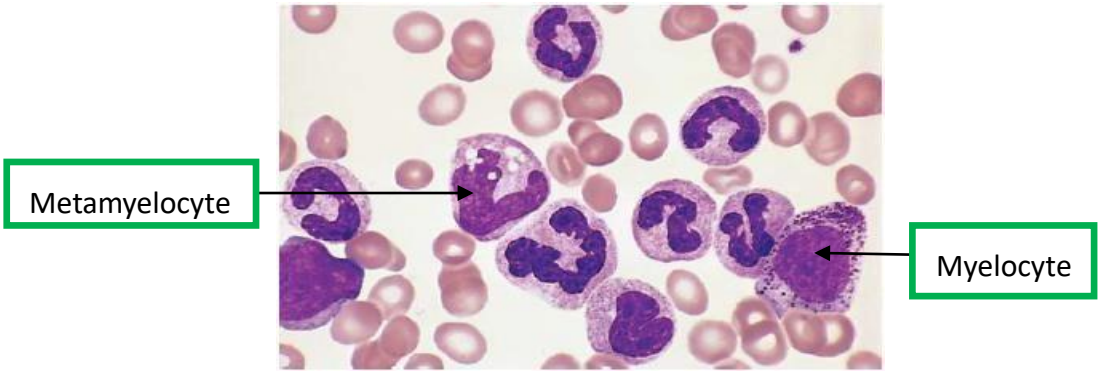
- All of these cells increase in number but what is the **MOST PROMINENT** cell in proliferation? →**MYELOID CELLS**.
- ***Symptoms***→ generally **non-specific**→ fatigue, heavy abdomen (due to splenomegaly) and weight loss.
- ***Treatment***→ **Imatinib** → tyrosine kinase inhibitor and specific for **Bcr/Abl mutation** (targeted therapy).
- CML starts as a chronic disease but with time , 50% of patients go into an **ACCELERATED PHASE**→ worsening of symptoms, higher WBC count, development of thrombocytopenia (instead of thrombocytosis), and sometimes even resistance to Imatinib.
- in other 50% of patients, 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).

remember: The Blast crisis is when **the blasts reach 20%** of the BM cells or the peripheral blood cells.

*spent phase : rarely develop (fibrotic BM)

- ***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).
  - ⇨**anemia** (instead of erythrocytosis)
  - ⇨**BM** biopsy → increased myeloid and megakaryocytes (**hypercellular**).
  - ⇨**Spleen** → Extramedullary Hematopoiesis (**EMH**).
  - ⇨**Blasts** count →**low**
  - ⇨**Leukemoid reaction** (looks like leukemia)→it's a benign condition where there is **high WBC** count and **shift to left .**

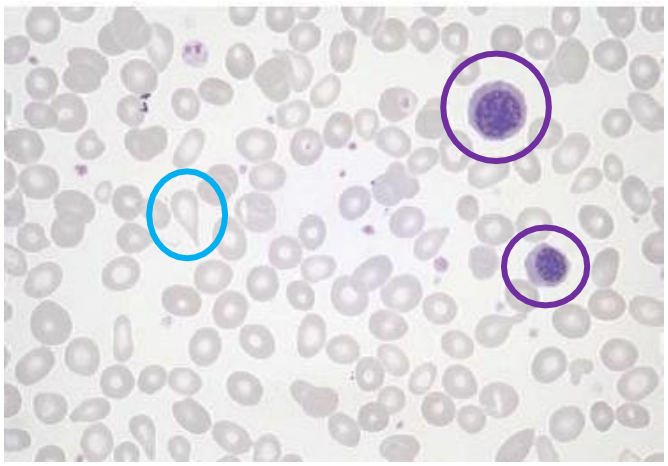
  Additional: (It occurs in **severe inflammation** like in sepsis or severe trauma. *It could also occur in CML, but how can we differentiate it ?* In CML, we have basophilia, eosinophilia, and thrombocytosis. Also, we can test for the Bcr/Abl gene mutation. The leukemoid reaction is benign and **reversible** so if we stop the inciting factor (like inflammation), the symptom will go away by itself.)



B. Primary Myelofibrosis

- **Primary** → the problem is in the BM itself.
- **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 (activation) in **MPL gene** (thrombopoietin receptor), 50% have mutation in CALR gene —> calreticulin —> activates MPL
- **HALLMARK OF THIS DISEASE** → **FIBROSIS**. This is because **neoplastic megakaryocytes** secrete platelet derived growth factor and **TGF-B**, which activates **fibroblasts** in BM to deposit **reticulin** and **collagen** fibers
- It also causes **ANGIOGENESIS** → Dilated blood vessels in BM
- Another characteristic → **RBC production is very impaired** → patients have moderate to severe **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**..

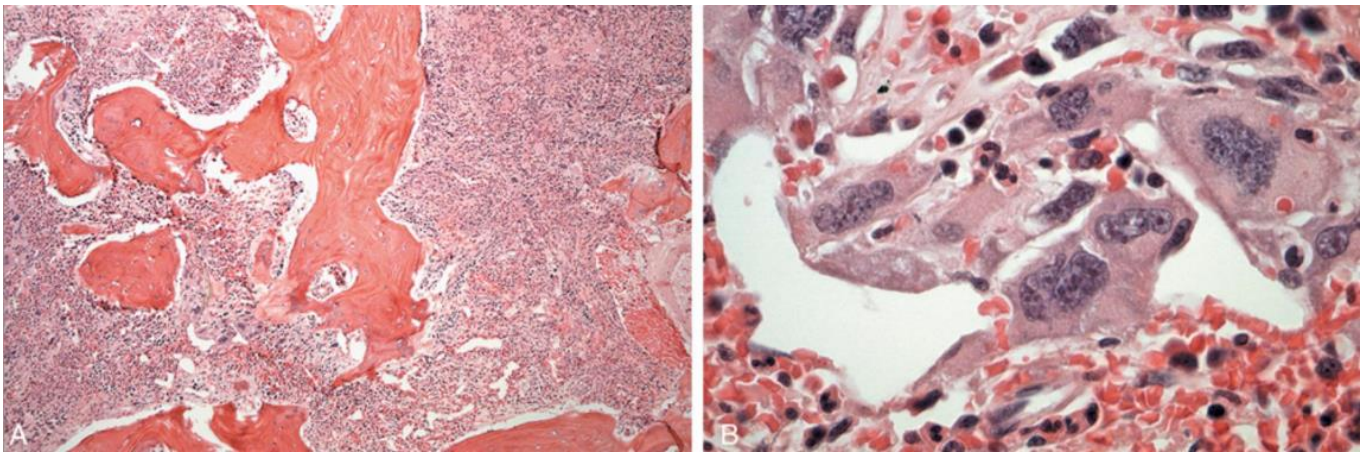
Morphology:



- ⇨Peripheral blood →**tear-drop cells**, **nucleated RBCs**, **shift to left** → **leucoerythroblastic anemia which is characteristic of myelofibrosis**.
- ⇨**WBC** → can be normal OR increased
- ⇨**Platelets** → High, but with time it becomes low due to fibrosis.

Clarification:

- ⇨**BM** → (1) **EARLY**: hypercellular (MPN) and focal fibrosis (2) **LATE**: hypocellular and extensive fibrosis.
- ⇨**DOMINENT CELLS**→**Megakaryocytes…**



PMF: left: hypercellular and thick bone trabeculae, right; clusters of abnormal megakaryocytes with large and hyperchromatic "cloud-like " nuclei. Note the dilated sinusoid

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** (due to thrombocytopenia or even in thrombocytosis the platelets not functioning) and/or **infection**.
- ⇨Worse outcome than CML and P Vera. 4-5 years survival
- ⇨Frequent transformation to AML (5-20%)

Treatment:

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

C. 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**

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.

Myelodysplastic Syndrome

- The main feature is **defective maturation**, **ineffective hematopoiesis**

  Extra : (the BM is full of hematopoietic stem cells, but they die there and cannot exit into the blood, this is similar to thalassemia in which we have ineffective erythropoiesis.

- There is a high risk for transformation to **AML**.
- BM is replaced by a clonal progeny of transformed stem cell(mutated stem cells) that still has the capacity to differentiate into three cell lines but with **abnormal morphology and function.** This is why the BM is full of cells but in the peripheral blood we have **cytopenia**.
- Hallmark of MDS: hypercellular BM, peripheral cytopenia and morphologic dysplasia.
- the tendency for accumulating more mutations and transform to AML

- ❖ Most cases are idiopathic, rarely follows chemo or radiotherapy **(therapy related)**
- ❖ Most patients are old.

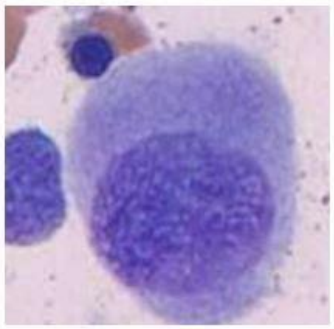
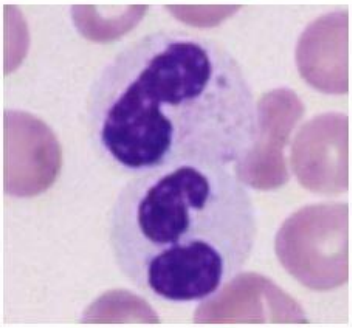
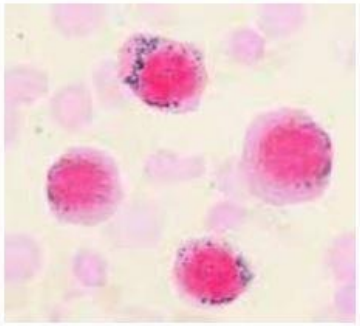
Pathogenesis:

- Chromosomal aberration (abnormality at the level of entire chromosome) in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8

Monosomy: single chromosome not doubled, Trisomy : extracopy chromosome

- Mutations in epigenetic factors that regulate **DNA methylation and histone modifications.**
- RNA splicing factors: abnormal RNA processing ⇨ **ring sideroblasts**.
- Transcription factors. (Mutated)
- 10% have P53 mutation. (Not common)

Morphology:

- ✓ Erythroid: **macrocytic anemia**, **megaloblastoid nuclei** (the chromatin is immature, and the cells are large), **ring sideroblasts** (iron accumulation inside the mitochondria of nucleated erythroid cells in the BM which appears as a blue ring around the nucleus). Right pic
- ✓ Myeloid: **decreased granulation**, **hyposegmented nuclei of neutrophils**. Middle pic
- ✓ Megakaryocytes: small, **hypolobated nuclei** (normally, it has multi nuclear lobes, but in this condition, it become monolobated nucleus).left pic

- ✓ Myeloblasts: can be increased, but they keep below 20% of nucleated cell.
  REMEMBER: If they reach 20%, we call it AML.

Symptoms:

- ✓ **Refractory anemia** (That means if you give iron, b12, EPO or steroids, anemia is not corrected), so, they usually treat them with **blood transfusion**.
- ✓ **Thrombocytopenia (bleeding), neutropenia (infection).**
- ✓ **Survival 9-29 months.**

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