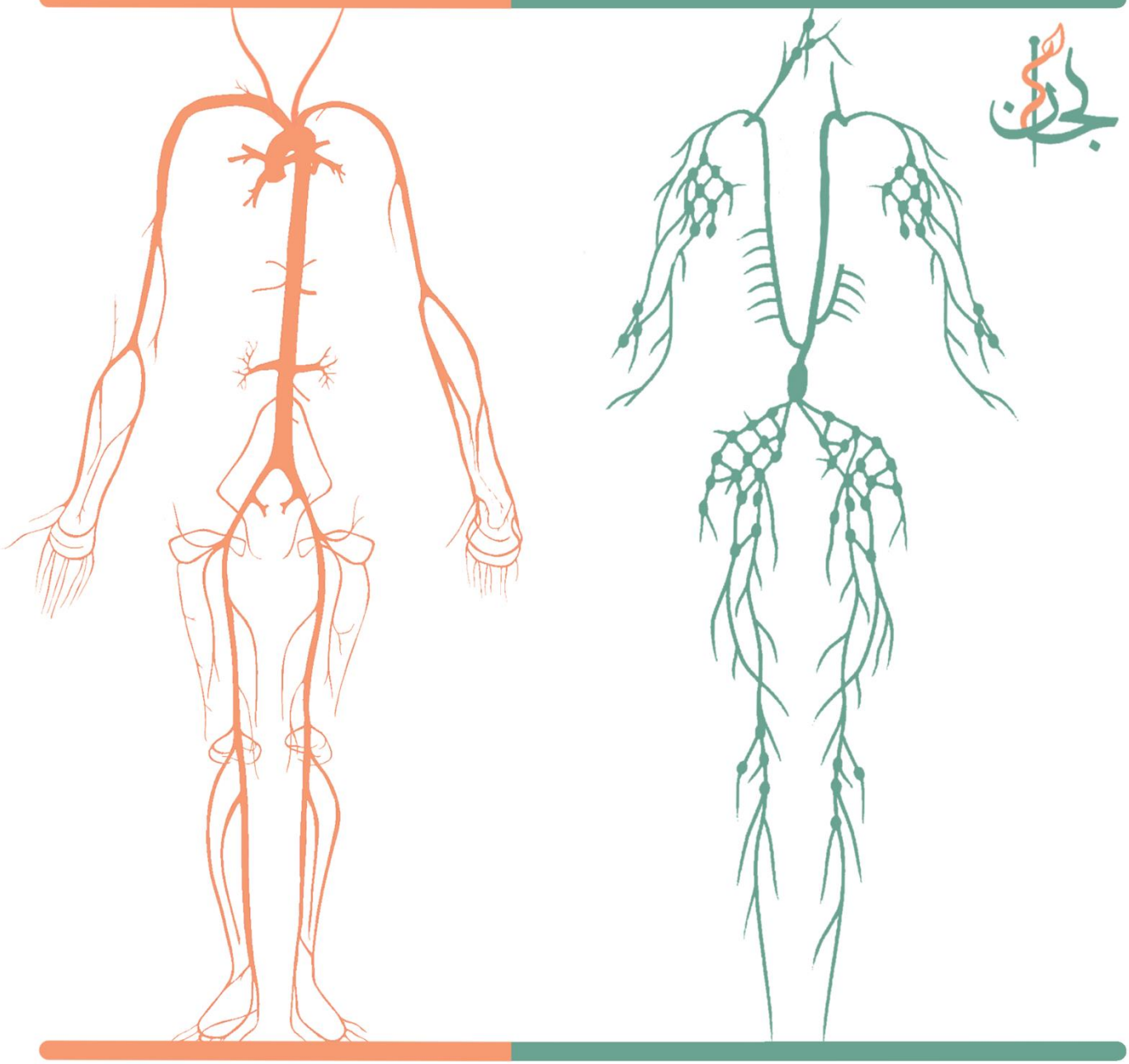
Pathology

HematoLymphatic



Title: Sheet 9 – Myeloid Neoplasms

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Myeloid Neoplasms

General features:

- ✓ They arise from **hematopoietic progenitor stem cells** in the bone marrow.
- ✓ They proliferate and efface normal hematopoietic cells resulting in a hypercellular bone marrow.

They are divided into 3 main categories:

1) Acute myeloid leukemia: Mutations lead **to impaired maturation** (cells are arrested at the most immature cell which is the myeloblast), and there is increased proliferation (myeloblast) ⇨ the bone marrow is filled with blasts.

2) Myeloproliferative neoplasms: There is **normal maturation**, increased proliferation => increased the number of normal cells in the bone marrow.

3) Myelodysplastic syndrome: **abnormal maturation, normal proliferation**.

- ❖ Peculiarly, **MPN and MDS** tend to transform to AML with time.

In the three categories, BM spaces are filled with hematopoietic stem cells (hypercellular).

The earliest stage of **carcinomas** (solid tumors) is called **Carcinoma in situ**, which means that the cells become neoplastic, but they are still in their normal place. On the other hand, **fluid neoplasms** have this condition in the earliest stage: **Clonal hematopoiesis of indeterminant prognosis (CHIP)**, it represents a precursor for AML and MDS, meaning that patients have normal cell count despite the presence of a clone with a mutation, so, with time they have an increased chance to become AML or MDS.

Acute Myeloid Leukemia

General features:

- This is one of the worst human cancers regarding the prognosis, it is a very aggressive neoplasm and it occurs at all age groups, but **more common in elderly**.
- It is a **Heterogenous disease** (not a single one) we have so many types within AML.

- The diagnosis is made by morphologic, immunophenotypic and karyotypic studies.
- Karyotypic study: It studies the mutations at the level of chromosomes (cytogenetic) and genes (molecular). This is the **WHO classification**, but in the previous one (**FAB classification**) they relied only on the morphology and immunophenotype.

WHO added karyotypic studies because **prognosis** depends most importantly on the type of mutations.

- Symptoms are **accelerated** (acute) and they become **significant and severe** within few weeks, patients become very ill and can die without treatment.
- Symptoms are related to BM destruction: **anemia, thrombocytopenia** (significant bleeding) and **neutropenia** (severe infections).

♣ Involvement of LN, spleen and solid organs is **rare**. But sometimes when occurs, it is called myeloid sarcoma (acute monoblastic leukemia) which is a subtype of AML. Monoblast tends normally to differentiate into a macrophage in tissues, so in this leukemia, they tend to go into solid organs and at that setting we call it **myeloid sarcoma** (tissue tumor of AML).

Pathogenesis:

- Mutations in genes of **transcription factors** required for maturation and differentiation of myeloblasts.
- Additional mutations in **tyrosine kinase pathways (RAS)** => **prolonged survival**
- **Epigenetic mutation** is common (20%); mutated isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with **myeloblast differentiation**.

Epigenetic mutation: A mutation that affects the function of the DNA without any changes in the codons.

AML WHO-Classification:

- **Therapy related AML** occurs after treatment with chemo or radiotherapy. For instance, if patient has a breast cancer and she received chemotherapy, she will have a risk for AML later on, so, we call it **therapy related AML**.

If the patient doesn't have a history of chemo or radiotherapy, then we test the **cytogenetic mutation**.

- **AML with recurrent cytogenetic mutation**. Recurrent means they commonly occur in AML. We have many types of those recurrent mutations, but we are not going to go through them because they are **many and complicated**. You just need to understand that some cytogenic mutations if they are positive then we call it as AML with this cytogenetic mutation as it affects the prognosis.

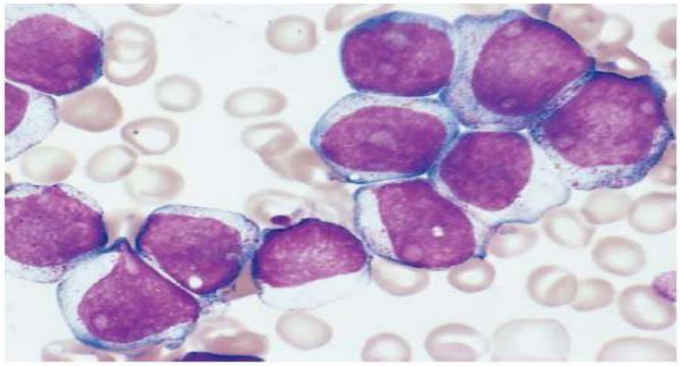
If the patient doesn't have these two, then we check for the presence of **myelodysplasia** (the abnormal shape of hematopoietic stem cells), if it is present then we call it:

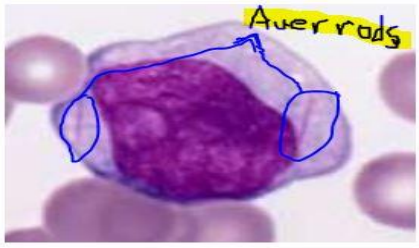
- **AML with myelodysplasia**. Patients with **MDS** can progress to **AML**. **AML with myelodysplasia** occurs either **de novo** and this is a very bad disease and when we examine the BM morphology, the hematopoietic stem cells look very abnormal. **OR** it **can be a complication of MDS** (less aggressive than the de novo one).

If no one of these is present, then it is **AML-Not otherwise specified**.

♣ Diagnosis of AML: **20% of blasts in peripheral blood OR bone marrow (of nucleated cells).**

Morphology:





- ✓ Myeloblasts are similar to lymphoblasts but they are larger and have more **amount of cytoplasm** (in comparison to lymphoblasts), **high N/C ratio**, **fine granules in cytoplasm** (granulocyte progenitor cells) in contrast to lymphoblasts which don't have granules, **fine chromatin (pale)**, **prominent nucleoli** (more than lymphoblast)

- ✓ Auer rods: small pink rods present in cytoplasm, represent **peroxidase enzyme**.
- ✓ Myeloblasts express **CD34**, **myeloperoxidase** (MPO), **CD13 and CD33**, the latter two expressed on the surface of all myeloid cells.
- ✓ They are negative for TdT and CD10.

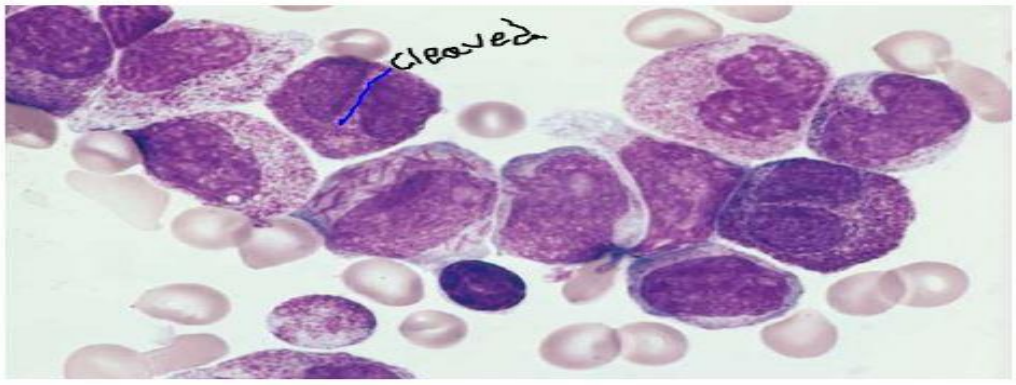
♣ Sometimes we see other cell lines: monoblast, erythroblast, megakaryoblast

Outcome:

Generally poor, <30% responds to chemotherapy (also recurrent rate is high), it is worse than ALL (even Acute lymphoblastic leukemia). The presence **of p53 mutation** makes the outcome even worse. **IDH inhibitors are new promising drugs.**

Acute promyelocytic leukemia

- ✓ Also called AML-M3 in the previous classification.
- ✓ Mutations formed at the level of promyelocyte, so, maturation is arrested at this point.
- ✓ Leukemic cells appear similar to promyelocytes (large cells with **heavy cytoplasmic granules**, **numerous Auer rods**, and they are negative for **CD34)**.
- ✓ Carry recurrent mutation: **t (15;17)** fusion between **PML gene** (chromosome **15**) with **alpha retinoic acid receptor (RARA)** on chromosome **17**. Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid (analogue of vit A).
- ✓ Treatment: we give high dose of a **vitamin A analogue called ATRA** (All trans-retinoic acid), which overcomes this block. Effect is synergistic with **arsenic trioxide** (degrades oncoprotein), and in this case you can treat 80% of cases.
- ✓ After giving the patients this treatment, promyelocytes will keep differentiating into neutrophils, and the neutrophils then die because they have short life span.
- ✓ We have a special situation in which malignant promyelocyte secrete **tissue factor**, causing **DIC**, so the patient might die from bleeding and not by the leukemia itself.



APL: malignant promyelocytes show **numerous cytoplasmic granules** and **Auer rods**. The nuclei are commonly cleaved (we call it "figure of eight" because it is similar to the number 8 in English).

Myelodysplastic Syndrome (chronic neoplastic disease)

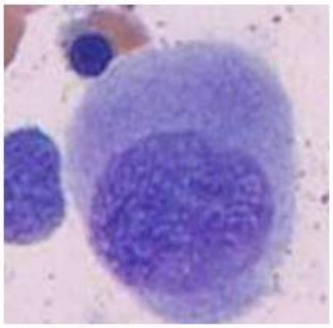
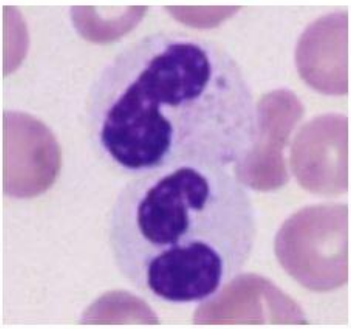
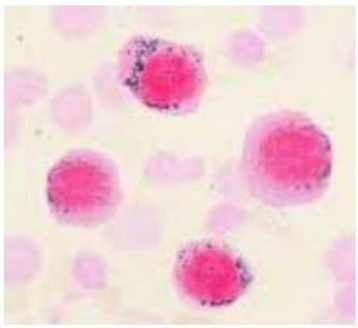
- The main feature is **defective maturation**, **ineffective hematopoiesis** (the BM is full of hematopoietic stem cells, but they die there and cannot exit into the blood, this is similar to thalassemia in which we have ineffective erythropoiesis.
- There is a high risk for transformation to **AML**.
- BM is replaced by a clonal progeny of transformed stem cell 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.
- 10 to 40% of patients end up with transformations into AML because they have the tendency for accumulating more mutations.
- Most cases are idiopathic, rarely follows chemo or radiotherapy **(therapy related)**
- Most patients are old.

Pathogenesis:

- Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8

- Mutations in epigenetic factors that regulate **DNA methylation and histone modifications.**
- RNA splicing factors: abnormal RNA processing ⇨ **ring sideroblasts**.
- Transcription factors.
- 10% have P53 mutation.

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).
- ✓ Myeloid: **decreased granulation**, **hyposegmented nuclei of neutrophils**.
- ✓ Megakaryocytes: small, **hypolobated nuclei** (normally, it has multi nuclear lobes, but in this condition, it become monolobated nucleus).
- ✓ Myeloblasts: can be increased, but they keep below 20% of nucleated cells either in the BM or in the peripheral blood. **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, neutropenia.**
- ✓ **Survival 9-29 months.**

GOOD LUCK