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# Pathology HLS

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# PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM-9

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# MYELOID NEOPLASMS

- Arises from hematopoietic progenitor stem cells in the BM.
- Neoplastic cells proliferate and efface normal hematopoietic cells which result in a hypercellular BM .
- Divided into:
- Acute myeloid leukemia: impaired maturation by certain mutations so the cells are arrested at the most immature cell which is the Myeloblast , increased proliferation (myeloblast) so the BM is filled with blasts not mature cells.
- Myeloproliferative neoplasms (MPN): normal maturation, increased proliferation (increased # of normal cells in the BM)
- Myelodysplastic syndrome (MDS) : abnormal maturation, normal proliferation
- Peculiarly, MPN and MDS can transform to AML with time
- BM is hypercellular in all myeloid neoplasms ( In these 3 categories, the BM is filled with hematopoietic stem cells HYPERCELLULAR. )

**NOTE**: normally with aging we have decrease in hematopoietic stem cells and relatively increase in fat but in these diseases (commonly affect old people) when we look at bone marrow we see hematopoietic stem cells in a large number which is not normal

- The earliest stages of carcinomas ( solid tumors) is called Carcinoma In Situ, which means that the cells become neoplastic but they are still in their normal place.Fluid neoplasms in their earliest stage have Clonal hematopoiesis of indeterminant prognosis (CHIP): represents a precursor for AML and MDS, patient has normal blood 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

- This is one of the worst human cancers regarding the prognosis, it is a very aggressive neoplasm ,Occurs at all age groups, but more common in elderly
- Heterogenous (not a single one, there is so many types within AML), diagnosis is made by morphologic, immunophenotypic and karyotype 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 they found out that the Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies)
- Symptoms are accelerated (Acute) , become significant within few weeks, patients become very ill & they can die without treatment.
- Symptoms are related to (BM destruction): anemia, thrombocytopenia (significant bleeding) and neutropenia (severe infection)
- Involvement of LN, spleen and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia) subtype of AML.

Monoblast tends normally to differentiate into a macrophage within tissues (histocytes) , 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 ( this is similar to ALL ,but we have different genes)
- Additional mutations in tyrosine kinase pathways (RAS) so the cells have prolonged survival.
- Epigenetic mutation (Affects the function of the DNA without any changes in the codons) is common (20%); mutation is isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation

# 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 pt. doesn't have a history of chemo or radiotherapy, then we test cytogenetic mutation

- AML with recurrent cytogenetic (at the level of chromosome) mutation (Recurrent means they commonly occur in AML. There are 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 these 2 were N-, then we check for the presence of myelodysplasia

- AML with myelodysplasia (abnormal shape of hematopoietic stem cells):

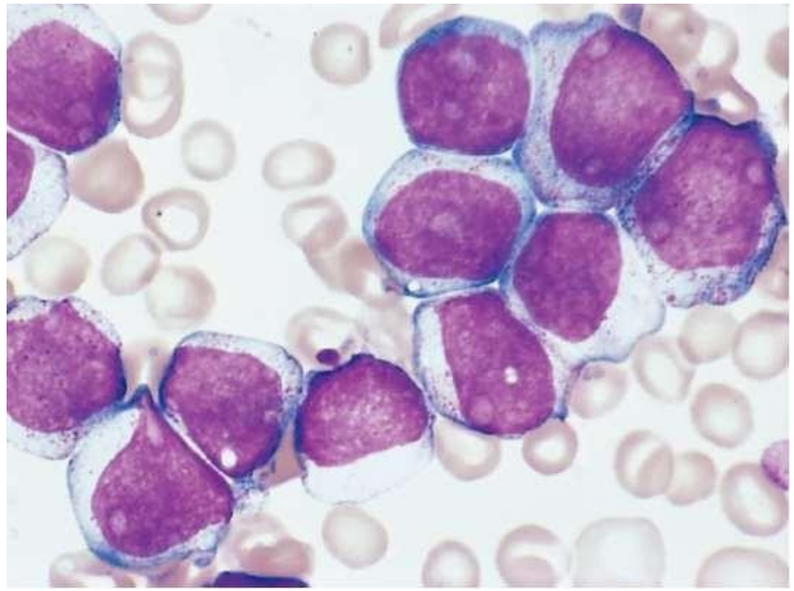
(Pt. with MDS can progress to AML) occurs de novo ( very bad disease and when we examine the BM morphology, the hematopoietic stem cells look very abnormal.)

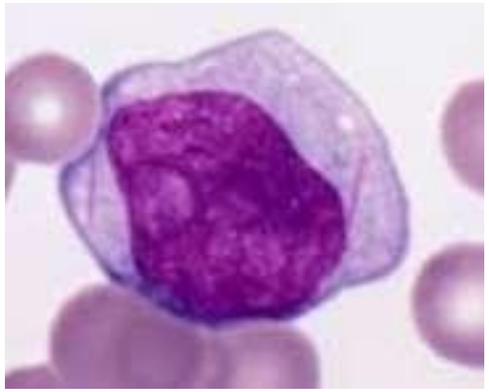
or complicates MDS ( less aggressive than de novo )

If there is no history of MDS & the morphology is N- for myelodysplasia it is called :

- AML-Not otherwise specified .

- Diagnosis of AML: 20% blasts in peripheral blood or bone marrow (of nucleated cells).





Myeloblasts are similar to lymphoblasts but they are larger and have more amount of cytoplasm (in comparison to lymphoblasts).

- Morphology: large cells, high N/C ration (it means the nucleus is more than 50% of the cell volume, but still we can see the cytoplasm more than the lymphoblast), fine granules in cytoplasm ( Granulocyte progenitor cells) in contrast to lymphoblasts which don't have granules, fine(pale) chromatin (not active), prominent nucleoli (more than in lymphoblasts)
- Auer rods (rare): small pink rods (needle shaped ,short) present in cytoplasm, represent peroxidase enzyme
- Myeloblasts express CD34, myeloperoxidase (MPO), CD13, CD33 Expressed on the surface of all myeloid cells

(Negative for TdT & CD10)

- Sometimes: monoblast, erythroblast, Rarely megakaryoblast

# OUTCOME

- Generally poor, <30% responds to chemotherapy (recurrent rate is high)
- Worse than ALL
- P53 mutation: worse outcome
- IDH inhibitors (new targeted therapy) are new promising drugs
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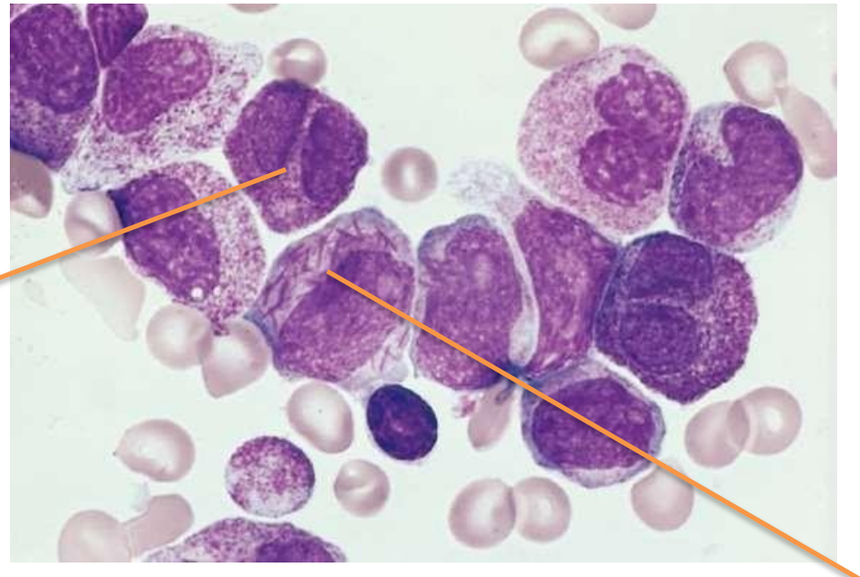
# ACUTE PROMYELOCYTIC LEUKEMIA

- Also called AML-M3 (on the FAB classification)
- Maturation is arrested at promyelocyte stage (the promyelocyte are the proliferating cells not the myeloblasts)
- Leukemic cells appear similar to promyelocytes (large cells with heavy cytoplasmic granules, numerous Auer rods, negative for CD34)
- Carry recurrent mutation: t(15;17) fusion between PML gene (chrom 15) with alpha retinoic acid receptor (RARA) on chrom 17. Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid. (Analog of vit. A ) so it is important for differentiation of myeloid cells.
- TREATMENT: High dose of All trans-retinoic acid (ATRA), a vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein)

- Before the discovery of this mutation Arsenic trioxide was helpful in treating these patients , Now it's given with ATRA (it has a synergistic effect) and 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.

- Malignant promyelocyte secrete tissue factor (activates both intrinsic & extrinsic pathways) , causing DIC so the pt. might die from bleeding not by the leukemia itself.

Cleaved nuclei



- APL: malignant promyelocytes show numerous cytoplasmic granules and Auer rods. The nuclei are commonly cleaved. (called figure of 8 because it's similar to number 8)

# MYELODYSPLATIC SYNDROME

Chronic neoplastic disease.

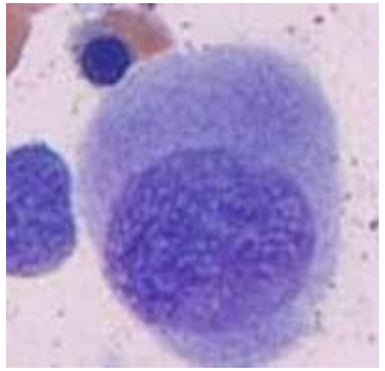
- Main feature is defective maturation, ineffective hematopoiesis (the BM is full of hematopoietic stem cells, but they die there and cannot exit into the blood, this is similar to thalassemia in which we have ineffective erythropoiesis) , high risk for transformation to AML
- BM is replaced by a clonal progeny of transformed stem cell that has an capacity to differentiate into 3 cell lines ( erythroid, myeloid & megakaryocytes) but with abnormal morphology and function, Therefore the BM is full of cells but in the peripheral blood we have cytopenia.
- Hallmark of MDS: hypercellular BM, peripheral cytopenia and morphologic dysplasia
- 10-40% of patients end up with transformations into AML because They have Tendency for accumulating more mutations and transform to AML called AML with myelodysplasia
- Most cases are idiopathic, rarely follows chemo or radiotherapy (therapy related)
- Most patients are old

# PATHOGENESIS

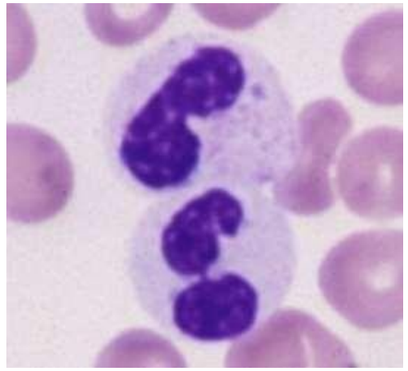
- Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8
- Mutations in epigenetic factors that regulate DNA methylation and histone modifications
- RNA splicing factors (mutations not in the codons nucleotide themselves instead in other steps): abnormal RNA processing (so the mRNA becomes abnormal and it ends up with mutant protein)→ ring sideroblasts
- Transcription factors
- 10% have P53 mutation

# MORPHOLOGY

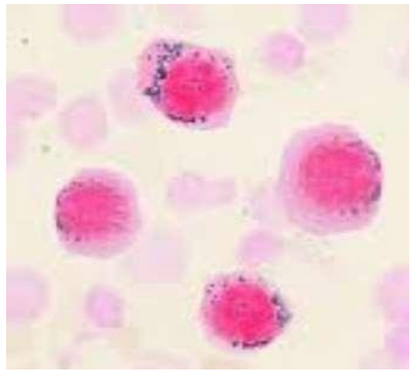
- Erythroid: macrocytic anemia, megaloblastoid nuclei (the chromatin is immature, and the cells are large), ring sideroblasts (accumulation of insoluble iron inside mitochondria of nucleated erythroid cells in the BM which appears as a blue ring around the nucleus).
- Myeloid: decreased granulation, 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 <20% of nucleated cells either in the BM or in the peripheral blood. If they reach 20%, we call it AML.



Megakaryocytes



Myeloid



Erythroid

# 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