Subject: HLS Pathology

Topic: Myeloid Neoplasms

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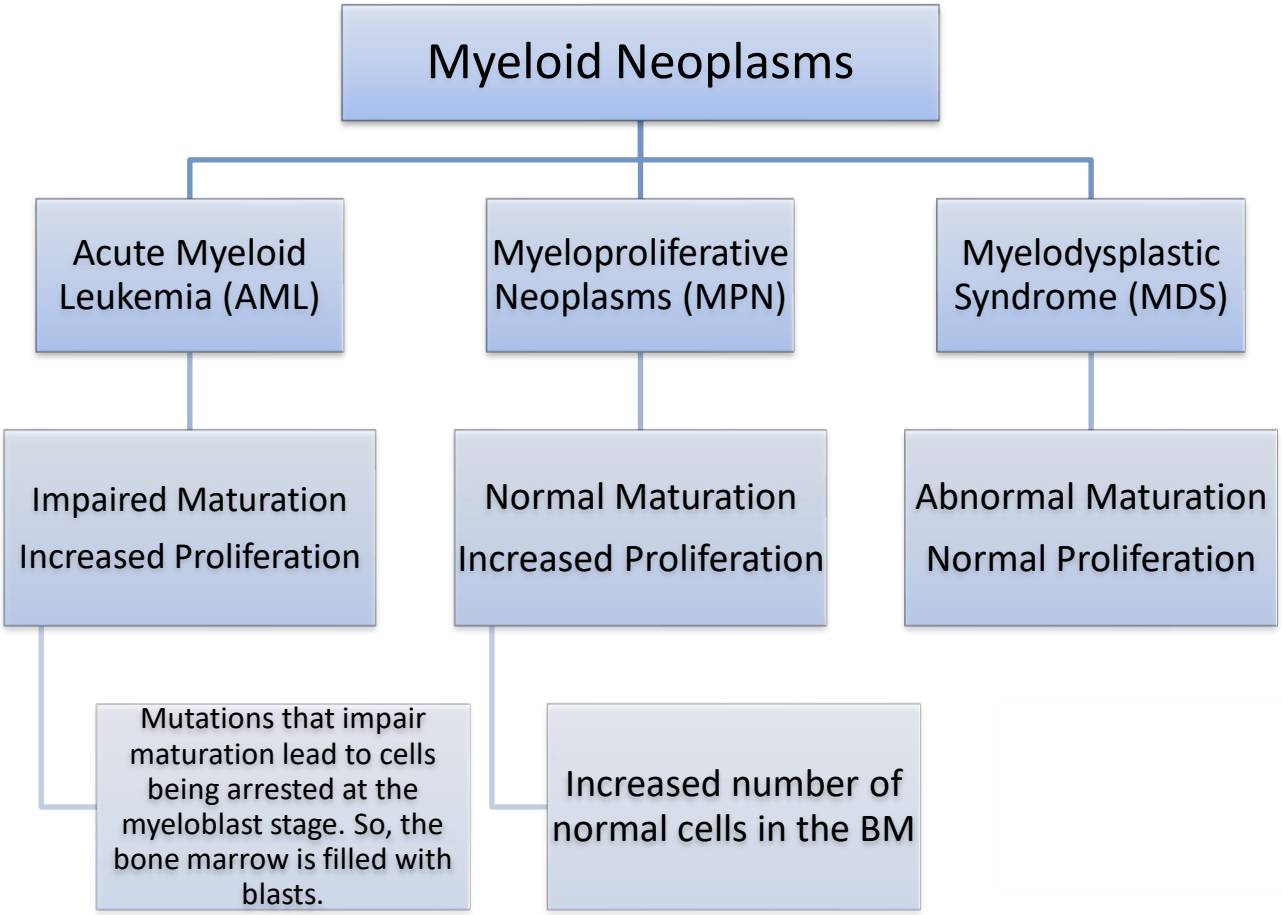
General Features of Myeloid Neoplasms:

1. They arise from hematopoietic progenitor stem cells in the bone marrow.
2. They proliferate and efface normal hematopoietic cells → Hypercellular bone marrow.



- MPN and MDS tend to transform to AML with time.
- Earliest stage of fluid tumors: Clonal hematopoiesis of indeterminant prognosis (CHIP) → Normal cell count but has a clone with a mutation → Precursor stage of AML and MDS → Increased chance to become these tumors.

Acute Myeloid Leukemia

General Info	Diagnosis
• One of the worst human cancers regarding the prognosis. • Aggressive neoplasm. • Occurs in all age groups, but more common in the elderly. • Heterogenous disease with many types.	• Made by morphologic, immunophenotypic, and karyotypic studies. (WHO Classification) • Karyotypic studies: Mutations at level of chromosomes (cytogenetic) and genes (molecular). Prognosis depends mostly on the type of mutations. • Diagnosis when there's: ○ 20% blasts in peripheral blood. (WBCs) ○ 20% blasts in BM (WBCs + nucleated RBCs)

Clinical Features

- Symptoms are accelerated (acute) → significant and severe within a few weeks → Patients can become very ill and die without treatment.
- Symptoms related to BM destruction: anemia, thrombocytopenia (significant bleeding), and neutropenia (severe infections).
- Involvement of the LNs, spleen, and solid organs is rare. If involved, this tissue tumor subtype of AML is called a myeloid sarcoma (acute monoblastic leukemia).

Pathogenesis

- Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts.
- Mutations in tyrosine kinase pathways (RAS) → Prolonged survival.
- Epigenetic mutations common (20%): Mutated isocitrate dehydrogenase → Production of an oncometabolite that blocks an enzyme that regulates the epigenome → Interference with myeloblast differentiation.

Outcome

- Generally poor
- <30% respond to chemotherapy.
- Recurrence rate is high.
- Worse than ALL.
- P53 mutation worsens outcome.
- IDH inhibitors are new promising drugs.

Morphology

- Myeloblasts are similar to lymphoblasts but are larger and have more cytoplasm.
- High N/C ration.
- Fine granules in cytoplasm (granulocyte progenitor cells).
- Fine chromatin (pale).
- Prominent nucleoli
- Auer rods: Small pink rods in cytoplasm, accumulation of peroxidase.
- Express CD34, myeloperoxidase (MPO), CD13, and CD33.
- Negative for TdT and CD10.
- Sometimes other cell lines (monoblast, erythroblast, megakaryoblast) present, but rare.

AML WHO Classification:

1. Therapy Related AML: Occurs after treatment with chemo or radiotherapy.
   ↓ *If the patient doesn't have a history of chemo or radiotherapy, we test for cytogenic mutations.*
2. AML with Recurrent Cytogenic Mutation: There are many recurrent mutations that commonly occur in AML. If a patient is positive for a cytogenic mutation, then they are classified as AML with that cytogenic mutation (as it affects prognosis).
   ↓ *If the patient doesn't fit these two classifications, we check for the presence of myelodysplasia.*
3. AML with Myelodysplasia: It occurs either:
   a. De novo: Very bad disease with abnormal hematopoietic stem cells in the BM.
   b. Complication of MDS: Less aggressive.
   ↓ *If none of these are present, this is:*
4. AML Not Otherwise Specified.

Acute Promyelocytic Leukemia

Also called AML-M3 in the previous classification.

Mutation	• Maturation arrested at level of promyelocyte. • Carries recurrent mutation t(15;17): Fusion between PML gene (chromosome 15) and alpha retinoic acid receptor (RARA) (17). • Fusion gene → Protein produced that inhibits action of retinoic acid (analogue of vit. A) → Promyelocyte maturation blocked.
Morphology	Leukemic cells appear similar to promyelocytes: Large cells, nuclei commonly cleaved, numerous cytoplasmic granules, numerous Auer rods, negative for CD34.
Treatment	• High dose of the vitamin A analogue ATRA (all trans-retinoic acid) overcomes the block on vit. A. • Effect synergistic with arsenic trioxide (degrades oncoprotein). In this case, you can treat 80% of cases.
Complication	Special situation: Malignant promyelocytes secrete tissue factor, causing DIC and death due to bleeding (not the leukemia).

Myelodysplastic Syndrome

General Info	• Chronic neoplastic disease • Defective maturation and ineffective hematopoiesis. • BM filled with transformed stem cells that have the capacity to differentiate into the three cells lines but with abnormal morphology and function. Cells die and can't exit into the peripheral bloodstream. • Cytopenia in the peripheral blood. • High risk for transformation to AML (10-40% end up with transformation into AML as they have the tendency to accumulate more mutations). • Most cases are idiopathic (rarely follows chemo or radiotherapy). • Most patients are old.
Hallmark	Hypercellular BM, peripheral cytopenia, and morphologic dysplasia.
Pathogenesis	• Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, and trisomy 8. • Mutations in epigenetic factors that regulate DNA methylation and histone modifications. • Mutations in RNA splicing factors → Abnormal RNA processing → Ring sideroblasts • Mutations in transcription factors • 10% have p53 mutation.
Morphology	• Erythroid: Macrocytic anemia, megaloblastoid nuclei (immature chromatin, large cells), ring sideroblasts (blue ring around nucleus due to iron accumulation inside mitochondria of nucleated erythroid cells). • Myeloid: Decreased granulation, hyposegmented nuclei of neutrophils.

	• Megakaryocytes: Small, hypolobated nuclei. • Myeloblasts: Can be increased, but must remain below 20% of nucleated cells in BM or peripheral blood (reaching 20% = AML).
Symptoms	• Refractory anemia – Treated with blood transfusions (not corrected with iron, B12, EPO, or steroids). • Thrombocytopenia and neutropenia. • Survival 9-29 months.