Myeloid neoplasm

- Arises from hematopoietic progenitor stem cells. BM is hypercellular.
1. Acute myeloid leukemia (AML): impaired maturation, increased proliferation (myeloblast).
2. Myeloproliferative neoplasms (MPN): normal maturation, increased proliferation
3. Myelodysplastic syndrome (MDS): abnormal maturation, normal proliferation
- MPN & MDS → AML
- Clonal hematopoiesis of indeterminant prognosis (CHIP): precursor for AML & MDS, patient has normal cell count

Acute myeloid leukemia

- Heterogenous, prognosis depends on type of mutations (molecular & cytogenic study: karyotype study)
- Symptoms are accelerated, related to anemia, thrombocytopenia & neutropenia.
- If it's involved LN, spleen & solid organ → myeloid sarcoma (acute monoblastic leukemia)
- Mutations in genes of TFs required for maturation of myeloblasts.
- // in tyrosine kinase pathways (RAS)
- Epigenetic mutation: isocitrate dehydrogenase (IDH) mutation → blocks enzyme of epigenome & interferes with myeloblast differentiation.

a. Therapy related AML: after chemo or radiotherapy treatment.
b. AML with recurent cytogenetic mutation.
c. AML with myelodysplasia: occurs de novo or complicates MDS.

- Diagnosis: 20% blasts in peripheral blood or BM.
- Large cells, ↑ N/C ratio, fine granules in cytoplasm, fine (pale) chromatin.
- Auer rods: small pink rods (needle shaped) represent peroxidase enzyme.
- Express CD34, myeloperoxidase (MPO), CD13 & CD33 in all myeloid cells
- Poor responds to chemotherapy.
- P53 mutation → worse outcome
- IDH inhibitors are new promising drugs

Acute promyelocytic leukemia (APL) "AML-M3"

- Maturation is arrested at promyelocyte stage (negative for CD34, heavy cytoplasmic granules, numerous Auer rods, cleaved nuclei "similar to number 8").
- t(15;17) fusion between PML gene & α-retinoic acid receptor (RARA) → chimeric fusion gene → inhibits retinoic acid action → blocks promyelocyte maturation.
- All trans retinoic acid (ATRA) "treatment": Vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein)
- Secrete tissue factor → DIC

Myelodysplastic syndrome

- Defective maturation, ineffective hematopoiesis, BM is replaced by a clonal progeny of transformed stem cell (differentiate into 3 cell lines):
① Erythroid: macrocytic anemia, megaloblastoid nuclei, ring sideroblasts (accumulation of insoluble iron inside mitochondria).
② Myeloid: ↓ granulation, hyposegmented nuclei of neutrophils.
③ Megakaryocytes: small hypolobated nuclei.
- Abnormal morphology & function —hallmarks→ hypercellular BM, peripheral cytopenia & morphologic dysplasia.
- Myeloblasts can be increased but < 20% of nucleated cells.
  If they reach 20% → AML
- Chromosomal aberration: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8.
- Mutations in epigenetic factors that regulate DNA methylation & histone modifications.
- RNA splicing factors: abnormal RNA processing → ring sideroblasts
- Refractory anemia, thrombocytopenia, neutropenia.
- Survival 9-29 months