Myeloproliferative Neoplasm (MPN)

- Normal maturation, proliferation is high.
- Active tyrosine kinase pathway, independent of the normal growth factors → hypercellular BM & peripheral blood cytosis.
- Neoplastic stem cells in liver & spleen → extramedullary hematopoiesis → hepatosplenomegaly.

* Subtypes of MPN:-

A. Chronic Myeloid Leukemia (CML):

- Harbor t(9;22) "Philadelphia chromosome" → fusion of Bcr/Abl genes → tyrosine kinase → prolonged cell survival.
- Leukemoid reaction: Leukocytosis (↑WBC > 100 K) & shift to left (presence of the precursor cells of the myeloid cells "not blasts" in the peripheral blood), occurs in severe inflammation. ↳ < 20%
- Basophilia, eosinophilia, thrombocytosis, iron deficiency anemia.
- Treatment: Imatinib (tyrosine kinase inhibitor, specific for Bcr/Abl mutation.
- Accelerated phase: worsening of symptoms, ↑WBC, resistance to imatinib, thrombocytopenia.
- Blast phase/crisis "when they reach 20% of BM or peripheral blood cells": transformation to acute myeloid leukemia (AML) or acute lymphoblastic anemia (ALL).

* Does Not have to follow this order (chronic → accelerated → blast).

B. Polycythemia Vera:

- Mutation in tyrosine kinase JAK 2 → hematopoietic cells become less dependant on growth factors.

* Hallmark: excessive proliferation of erythroid, megakaryocytes & myeloid (Panmyelosis).

- Erythrocytosis → polycythemia —negative feedback→ ↓ erythropoietin.
- Hematocrit > 60%
- Plethora (skin full of erythema), cyanosis (deoxygenated Hb), pruritis, peptic ulcer (Leukocytosis → basophilia → ↑ histamines).
- Thrombosis → tissue infraction — Bleeding in GIT.
- Gout (↑ uric acid)
- Spent phase: after 10 years → BM become fibrotic → hematopoiesis shifts to spleen.
- Blast crisis: rare
- Treatment: phlebotomy, JAK 2 inhibitor

C. Primary Myelofibrosis: "Worst type of MPN"

- Overt "severe" BM fibrosis → ↓ hematopoiesis
- JAK-STAT signaling pathway is active
- Mutation in JAK 2, MPL (thrombopoietin receptor)
- Neoplastic megakaryocytes → ↑ TGF-B → ↑ fibroblasts → ↑ reticulin & collagen → remove hematopoiesis & fat cells → angiogenesis → large vascular space.
- BM: hypercellular then hypocellular
- Cytosis then cytopenia
- Tear drop cells + nucleated RBCs + shift to left → leucoerythroblastic anemia
- Massive splenomegaly, gout, bleeding, 4-5 years survival
- WBC: normal or increased
- Platelets: high then low
- Treatment: JAK 2 inhibitor → ↓ splenomegaly

D. Essential thrombocythemia:

- Thrombocytosis, leukocytosis
- JAK2 mutation, No BM fibrosis
- Splenomegaly, good outcome

Langerhans Cell Histiocytosis (LCH)

- Neoplasm of dendritic cells
- Langerhans (dendritic) cells express CD1a & Langerin (attached to birbeck granules)
  - ↳ become large & vaculated "similar to macrophages"
- Mutation in serine/threonine kinase BRAF → hyperactivity of this kinase.

* Categories of LCH:-

A. Multisystemic LCH:

- Multiple skin (cutaneous) lesions, composed of langerhans cells.
- Hepatosplenomegaly & lymphadenopathy.
- Pulmonary & osteolytic lesions.
- Extensive bone marrow infiltration → myelophthisic anemia & pancytopenia
- Treatment: chemotherapy

B. Unisystem LCH (Eosinophilic granuloma):

- Affects a single organ, most commonly bone.
- Proliferating LCs are admixed with numerous eosinophils, lymphocytes, plasma cells & neutrophils.

1- Unifocal: asymptomatic, treatment: surgical excision

2- Multifocal: affects the skull bone (clavaria bone), extends to pituitary gland → diabetes insipidus & exophthalmos "neural damage"
→ Hand-schuller-christian triad

treatment: chemotherapy, spontaneous regression.