* MDS → BM replaced by clonal progeny
  - retain capacity to proliferate ⇒ ineffective & disordered Manner
  - BM: Hyper- or Normocellular
  - peripheral Blood: cytopaenias.
  - Genetically unstable → Mutations (10-40%) → AML
    - idiopathic
    - after Chemotherapy / radiation
  - Errors in
    - Epigenetic factors
    - RNA splicing
    - Transcription factors
    - ↑ Ring Sideroblasts ↓
  - also in 10%: TP53 errors (Loss of function).
* Abnormalities:
  1) Monosomies of 5 & 7
  2) deletions of 5q & 7q & 20q
  3) Trisomy of 8
* 5q- MDS: → Adult women
  - Refractory Anaemia.
  - suspected on: BM-core Biopsy.
    confirmed by: Routine Cytogenic Study.
  - small & Monolobated Megakaryocytes
1 * Megaloblastoid Erythroid Precursors
2 * Ring Sideroblasts.
3 * Granulocytes w/ Abnormal Granules.
4 * Small Megakaryocytes.

* Cause: Anaemia, Haemorrhages, infections.
* Response to chemotherapy: POOR
* Survival: 9-29 Months.

Myeloproliferative Neoplasms

- Activated Tyrosine-Kinase / GF independence
  - Therapy: Tyrosine-Kinase Inhibitors
- Mutations: ① BCR-ABL → in CML
  - ② JAK2 (tyr. kin.) → all Polycythemia Vera, 50% of Primary Myelofibrosis & Essential Thrombocythaemia
  - ③ PDGFR-α & -β
- * spent phase (primary Myelofibrosis)
- * blast crisis (acute Leukaemia)

① Chronic Myeloid Leukaemia

- 4th-5th Decade (BCR-ABL; ~~t(9;22)~~ Ph. Chr. (Balanced; BCR @ 22 + ABL from 9)
  - [CML; 25% of Adult B-Cell-ALL & small subset of AML]
- only excessive production of normal BCs (granulocytes & platelets).
  - >100 K Leukocytes. (Hypercellular BM)
- circulating cells:
  1. * Myelocytes
  2. * Metamyelocytes
  3. * Neutrophils.
- Extramedullary Haematopoiesis; splenic infarcts/splenomegaly.
- Slow progression, survival: 3 years
- 50% → Blast crisis → 70%: Resemble pre-B-ALL
  - 30%: Resemble AML

Less commonly → "Spent" → BM fibrosis.

② Polycythaemia Vera.

- JAK2 downstream ~~Erythropoietin~~ (low levels of EPO) → Panmyelosis (esp ↑RBC)
- hepatomegaly → Congestion + Extramedullary Haematopoiesis
- Splenomegaly → congestion
- Thromboses & infarction & Haemorrhage.
- Dysfunctional platelets
- Peripheral Blood = Basophilia
- plethoric + cyanotic facies.
- Histamine → pruritis + peptic ulceration
- HTN, headache, dizziness
- GIT, haematemesis, Melena
- symptomatic gout
- HCT > 60%
  - WBC ~ 50,000
  - platelets > 400,000

30% → Thrombosis (Brain & heart)

* Hepatic Vein Thrombosis (Budd-Chiari Syndrome)
* Epistaxis & Gum bleeding
* No treatment → Median Phlebotomy → 10 yrs.
  - ⇩
  - "spent phase" 15-20%.
* Blast crisis less frequently (AML).

Koshin Color

③ Primary Myelofibrosis

- obliterative Marrow fibrosis
- cytopaenias, extramedullary Haematopoiesis.
- JAK-STAT → JAK2 ~~→ MPL Activation~~ (50-60%)
  - MPL-Activation (thrombopoietin Receptor) (1-5%)
- fibrogenic factors; released by: Neoplastic Megakaryocytes.
  - PDGF & TGF-B ⇒ "fibroblast Mitogens" ↑.
- 5-20% ⇒ AML

1. * poikilocytosis ; teardrop cells (dacrocytes).
2. * Nucleated Erythroid precursors.
3. * Immature WBCs (Myelocytes & Metamyelocytes).
4. * Leukoerythroblastosis
5. * Large platelets.

>60yo, Anaemia + splenomegaly
fatigue, weight loss, night sweats

Secondary gout.

* Bleeding / thrombosis
* BM Biopsy (diagnosis).
* 4-5 yr survival
* JAK2 inhibitors: ↓ splenomegaly & symptoms.
* Haematopoietic stem-cell transplantation.