Pathology of hematolymphoid system
Myeloproliferative Neoplasms
Myelodysplatic syndrome

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MYELOPROLIFERATIVE NEOPLASMS

- Was known as the myeloproliferative disorder
- Group of diseases where bone marrow became neoplastic

- Maturation is normal, but proliferation is high
  Mature RBCs + WBCs are normal but the immature are high
- Permanently active tyrosine kinase pathway, independent from growth factors
  mutation in tyrosine kinase pathway result in permanent growth patern of the disease
- BM is hypercellular, peripheral blood shows cytosis → WBC, RBC, platlets
  During aging hematopoitic stem cells are replaced by fat
- Neoplastic stem cells in MPN often seeds to spleen, liver and occasionally LNs, causing extramedullary hematopoiesis and thus hepatosplenomegaly

patients usually in old age or middle age but hematopoitic cells still fill the bone marrow

- Tendency to develop a "spent phase" after a long time, characterized by bone marrow fibrosis Decreased number of cells.

* Tendency to transform to AML
  Acute myloid leukemia
  ↳ due to accumulation of mutations

CHRONIC MYELOID LEUKEMIA

- Most common MPN
- Peak incidence is 4th-5th decade Can occure in any age even in Children.
- Harbor t(9;22) (Philadelphia chromosome) results in fusion of Bcr/Abl genes and production of a tyrosine kinase that results in prolonged cell survival
  - ↳ potent
- Mutation is present in all BM cells (myeloid, erythroid and megs)
  - ↳ Hematopoitic Stem cells with different effect on each
- Symptoms:chornic non-specific: fatigue, heavy abdomen, weight loss
  - ↳ splenomegaly
- Imatinib: tyrosine kinase inhibitor, specific for bcr/abl mutation
  - ↳ Affect only neoplastic cells
- Accelerated phase: develop in 50% of patients:: worsening of symptoms, higher WBC count, thrombocytopenia, resistance to imatinib
  - ↳ + worsining anemia
- Blast crisis: in the other 50% of patients, transformation to acute leukemia (AML>ALL)
  - ↳ Blasts become dominant
  - myloblasts + lymphoblasts → acute leukemia

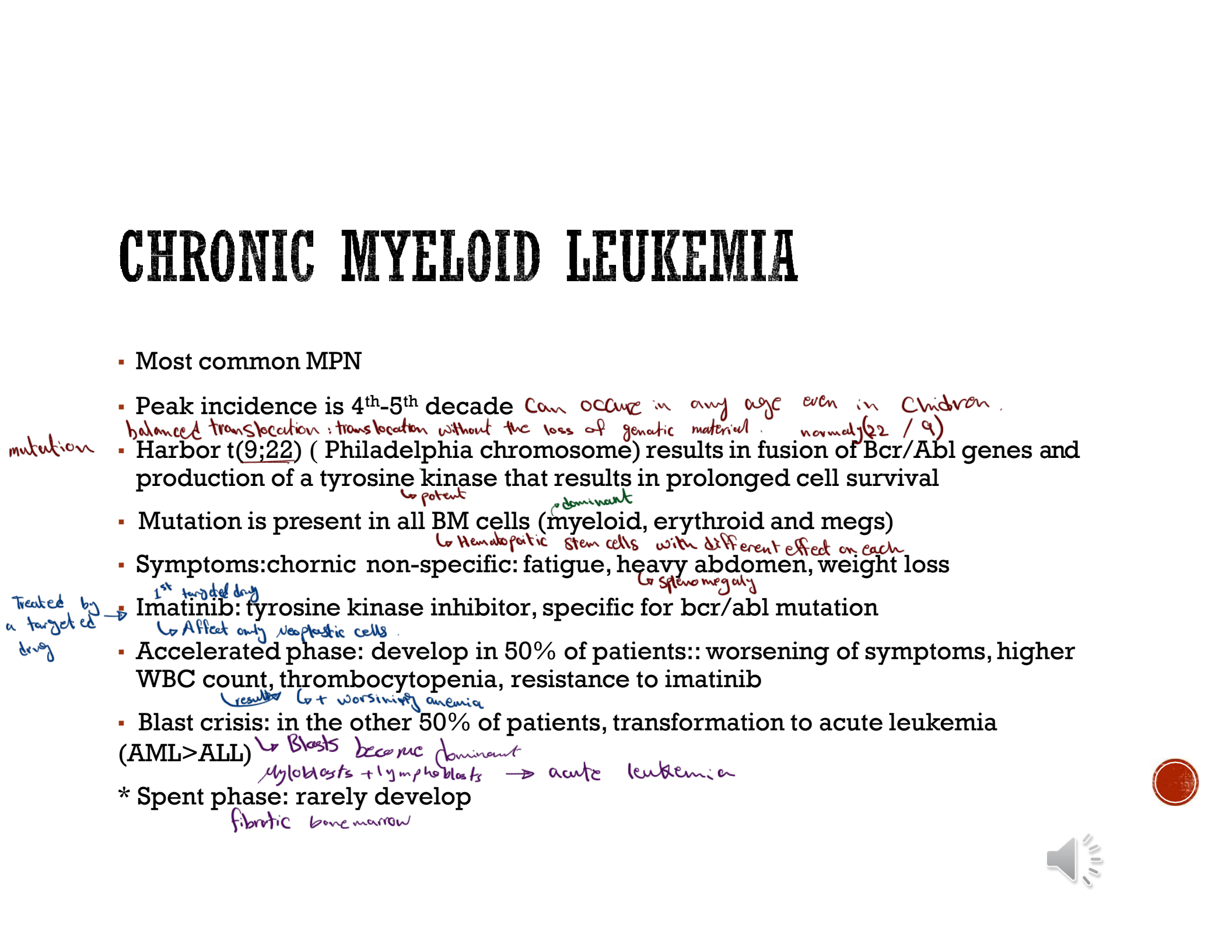
* Spent phase: rarely develop

fibrotic bone marrow

balanced translocation : translocation without the loss of genetic material. normaly(22 / 9)

mutation

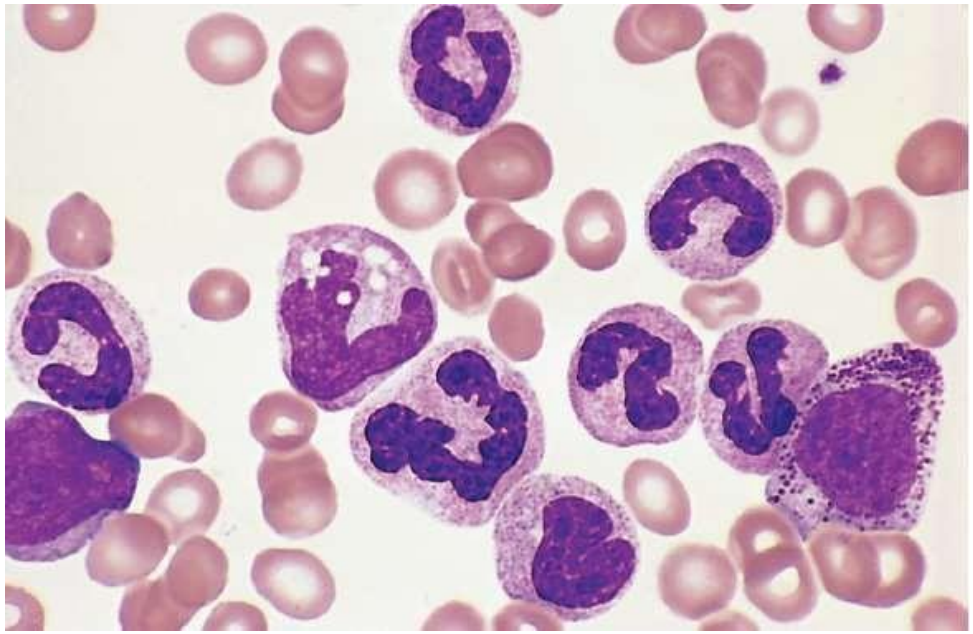
Treated by a targeted drug → 1st targeted drug



MORPHOLOGY OF CML

myloid cells

- Leukocytosis, can be >100K
- Shift to left
- Basophilia, eosinophilia
- Thrombocytosis At begining is common
- Anemia
- BM: increased nyeloid and megs
- Spleen: EMH
- Blasts: low
- Leukemoid reaction: high WBC and shift to left, occurs in severe inflammation



PRIMARY MYELOFIBROSIS

- Overt BM fibrosis, reducing capacity for hematopoiesis, leads eventually to cytopenia and massive EMH
  - massive splenomegaly
- JAK-STAT signaling pathway is active in all cases
- 50% have mutation in JAK2, 5% in MPL gene (thrombopoietin receptor), 50% have mutation in CALR gene → calreticulin → activates MPL
- Neoplastic megakaryocytes secrete platelet-derived growth factor and TGF-B, which activates fibroblasts in BM to deposit reticulin and collagen fibers, also causes angiogenesis
- RBC production is impaired, RBCs appear as tear-drop, patients have moderate to severe anemia

Mutation

seen in Polycythemia vera

Activates Megacaryocytes

It's unknown dif. patients have dif. mutations. or why JAK2 resulted in primary myelofibrosis not poly.

Dominat and very active.

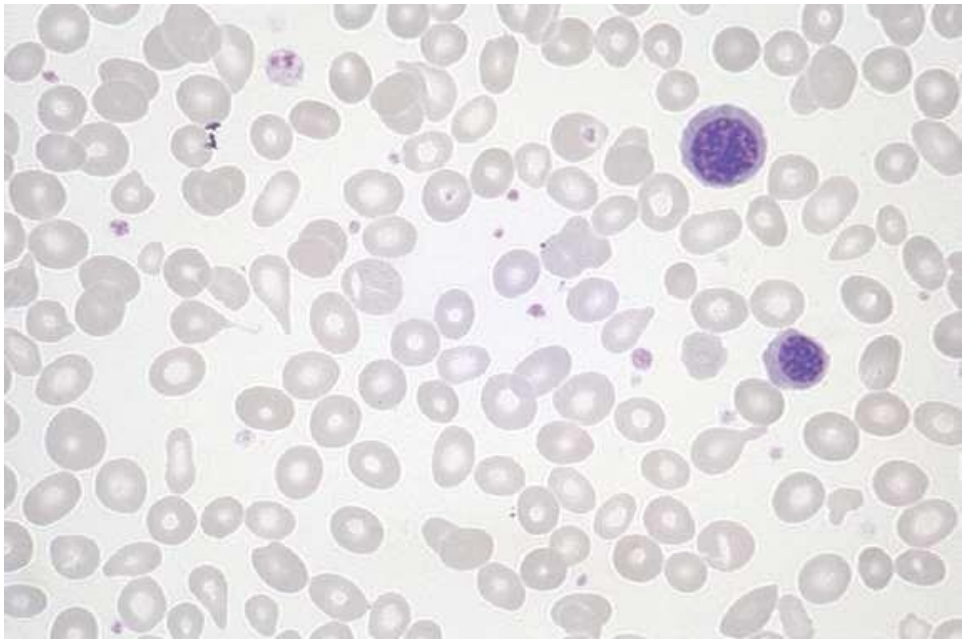
TGF-B

by Proliferation of endothelial cells → dilated small blood vessels.

more impairment

MORPHOLOGY

- Peripheral blood: tear-drop cells, nucleated RBCs, shift to left (leukoerythroblastic anemia)
- WBC: can be normal of increased
- Plt: high, then low

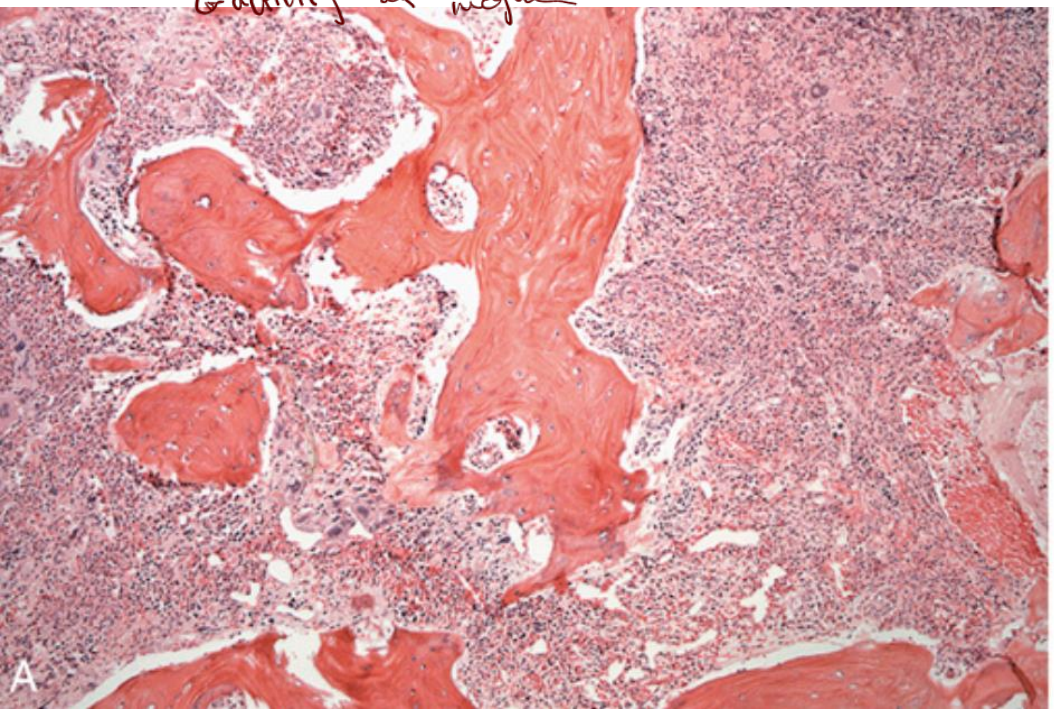


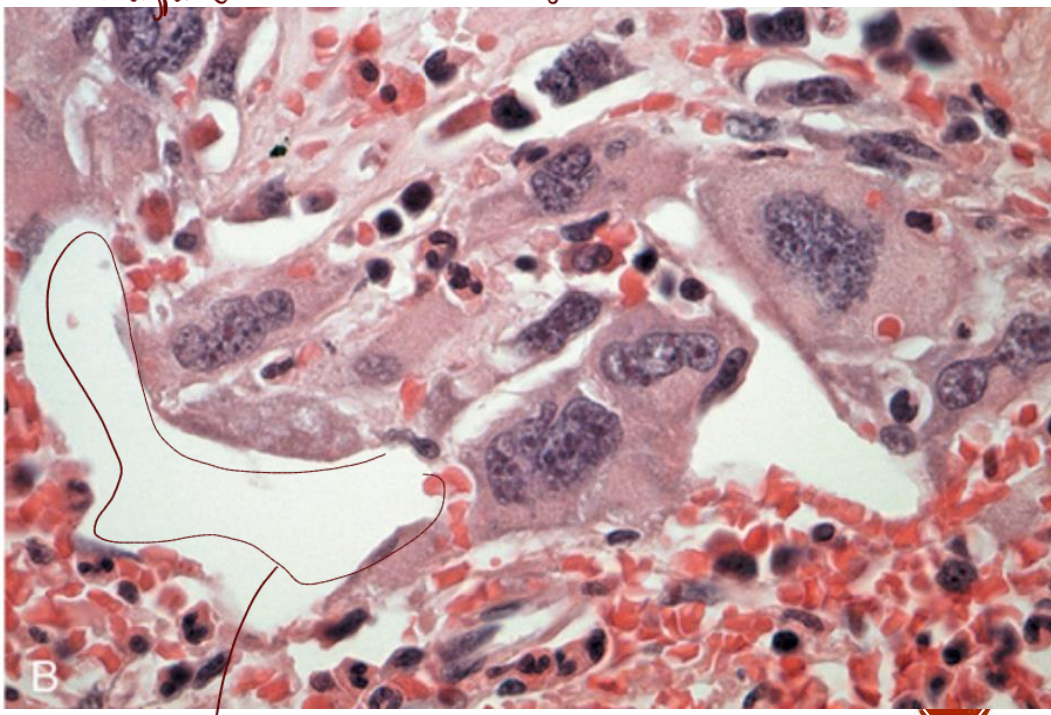
PMF: left: hypercellular and thick bone trabeculae, right: clusters of abnormal megakaryocytes with large and hyperchromatic "cloud-like" nuclei. Note the dilated sinusoid

* filled with Hematopoitic cells (no fat cells)
* Bone osteoid material is thicker than normal (activity of mega)

* High power view
* alot of mega -- that are large
* larger nuclei about 50% of cell volume
  * hyperchromatic and irregular.

cloud like





Sinusoid due angiogenesis and the activity of mega...

CLINICAL FEATURES

- Non-specific symptoms, weight loss, anemia, massive splenomegaly, gout, bleeding, infection
- Worse outcome than CML and P Vera. 4-5 years survival
- Frequent transformation to AML (5-20%)
- JAK2 inhibitor: decreases splenomegaly and symptoms

ESSENTIAL THROMBOCYTHEMIA

Megakaryocytic proliferation and thrombocytosis

- Predominantly thrombocytosis (occasional leukocytosis)
- JAK2 mutation is sometimes positive, but NO bone marrow fibrosis
- Splenomegaly is positive in 50%
- Good outcome

The last disease of the myloproliferative diseases is the PVera.

MYELODYSPLASTIC SYNDROME MDS

- Main feature is defective maturation, ineffective hematopoiesis, 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 but with abnormal morphology and function
- Hallmark of MDS: hypercellular BM, peripheral cytopenia and morphologic dysplasia
- Tendency for accumulating more mutations and transform to AML
- Most cases are idiopathic, rarely follows chemo or radiotherapy (therapy related)
- Most patients are old

PATHOGENESIS

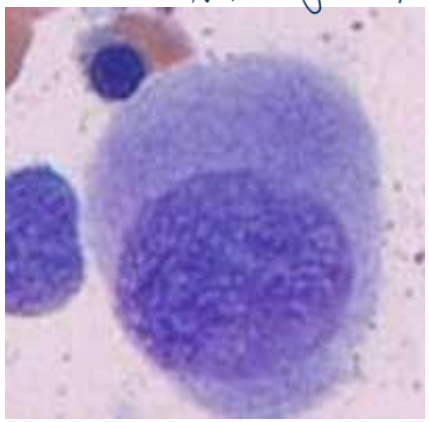
very variable

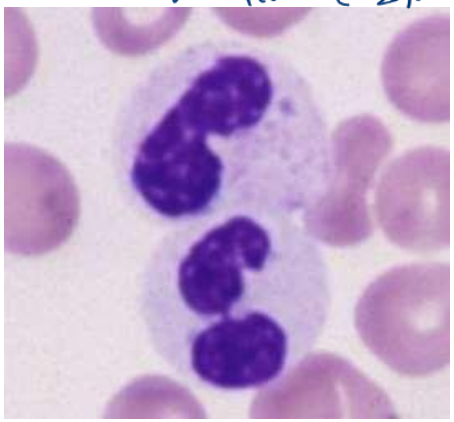
- Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8 (Single chromosome)
- Mutations in epigenetic factors that regulate DNA methylation and histone modifications
- RNA splicing factors: abnormal RNA processing → ring sideroblasts
- Transcription factors (can be mutated)
- 10% have P53 mutation

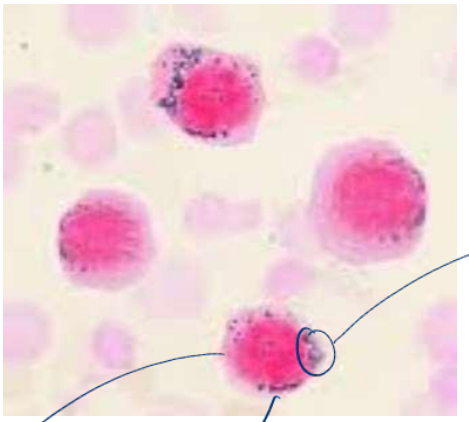
(G mutation special for RNA splicing)

MORPHOLOGY

- Erythroid: macrocytic anemia, megaloblastoid nuclei, ring sideroblasts (iron accumulation inside mitochondria)
- Myeloid: decreased granulation, hyposegmented nuclei of neutrophils
- Megkaryocytes: small, hypolobated nuclei
- Myeloblasts: can be increased, but <20% of nucleated cells







Immature

Almost identical to Megaloblastic anemia

1–2 lobes

Normaly 2%

↳ if reached 20% → AML

Iron Accumulat in the Mitochondria around the nucleay

Ring Sideroblast

Nucleated RBCs with a ring of blue dots

SYMPTOMS

- Refractory anemia, thrombocytopenia, neutropenia
- Survival 9-29 months