Pathology of hematolymphoid system
Myeloproliferative Neoplasms
Myelodysplatic syndrome

Dr. Tariq Aladily
Professor
Department of Pathology
The University of Jordan
tnaladily@ju.edu.jo

School of Medicine

MYELOPROLIFERATIVE NEOPLASMS

- Maturation is normal, but proliferation is high
- Permanently active tyrosine kinase pathway, independent from growth factors
- BM is hypercellular, peripheral blood shows cytosis
- Neoplastic stem cells in MPN often seeds to spleen, liver and occasionally LNs, causing extramedullary hematopoiesis and thus hepatosplenomegaly
- Tendency to develop a "spent phase" after a long time, characterized by bone marrow fibrosis

* Tendency to transform to AML

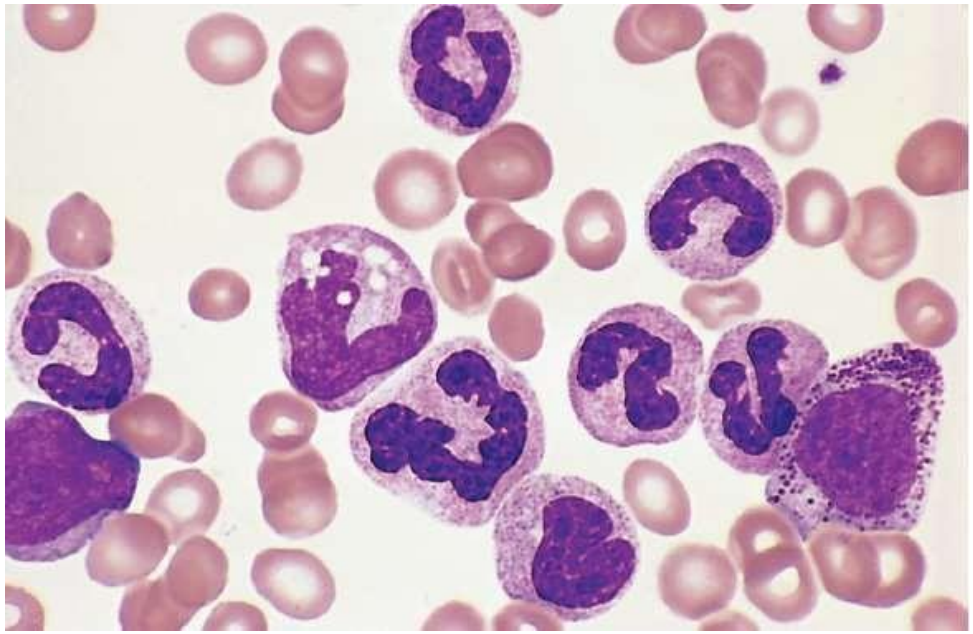
CHRONIC MYELOID LEUKEMIA

- Most common MPN
- Peak incidence is 4^{th}-5^{th} decade
- 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
- Mutation is present in all BM cells (myeloid, erythroid and megs)
- Symptoms:chornic non-specific: fatigue, heavy abdomen, weight loss
- Imatinib: tyrosine kinase inhibitor, specific for bcr/abl mutation
- Accelerated phase: develop in 50% of patients:: worsening of symptoms, higher WBC count, thrombocytopenia, resistance to imatinib
- Blast crisis: in the other 50% of patients, transformation to acute leukemia (AML>ALL)

* Spent phase: rarely develop

MORPHOLOGY OF CML

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

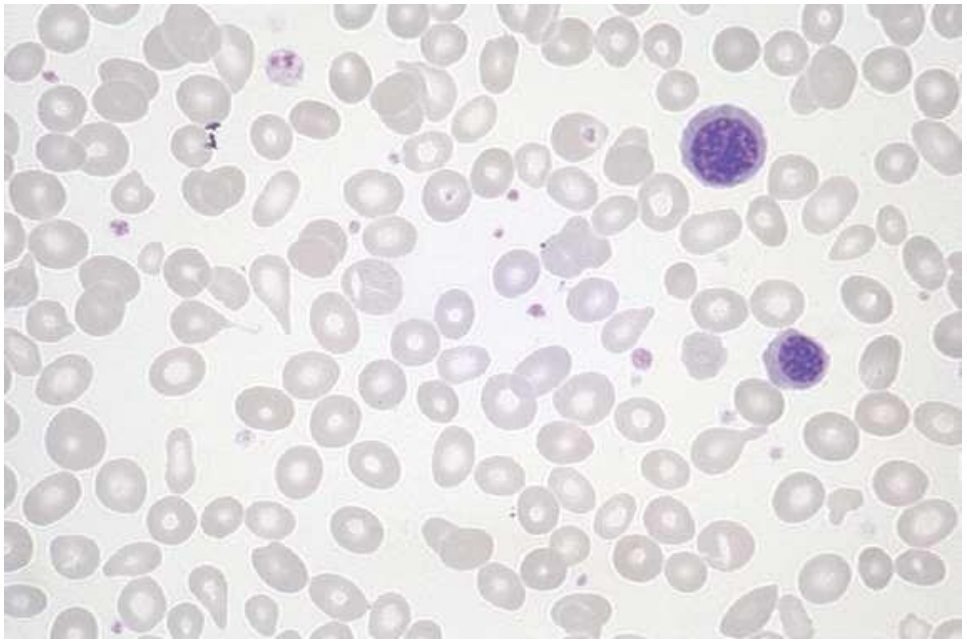


PRIMARY MYELOFIBROSIS

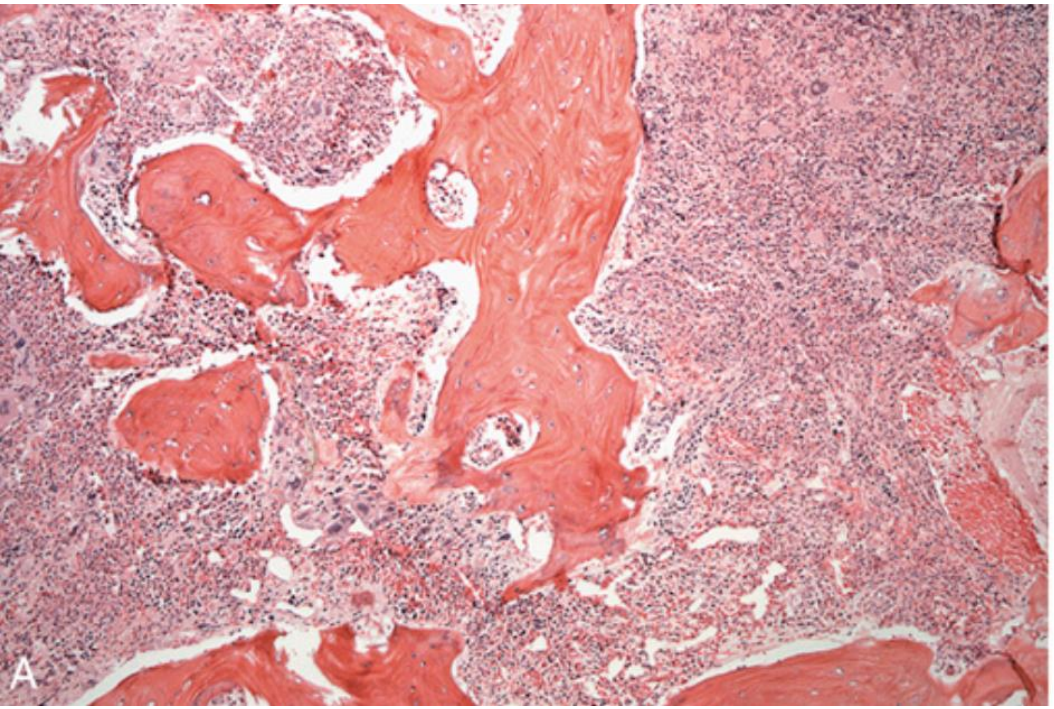
- Overt BM fibrosis, reducing capacity for hematopoiesis, leads eventually to cytopenia and massive EMH
- JAK-STAT signaling pathway is active in all cases
- 50% have mutation in JAK2, 5% in MPL gene (thrombopoietin receptor), 50% have mutation in CALR gene → calreticulin → activates MPL
- Neoplastic 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

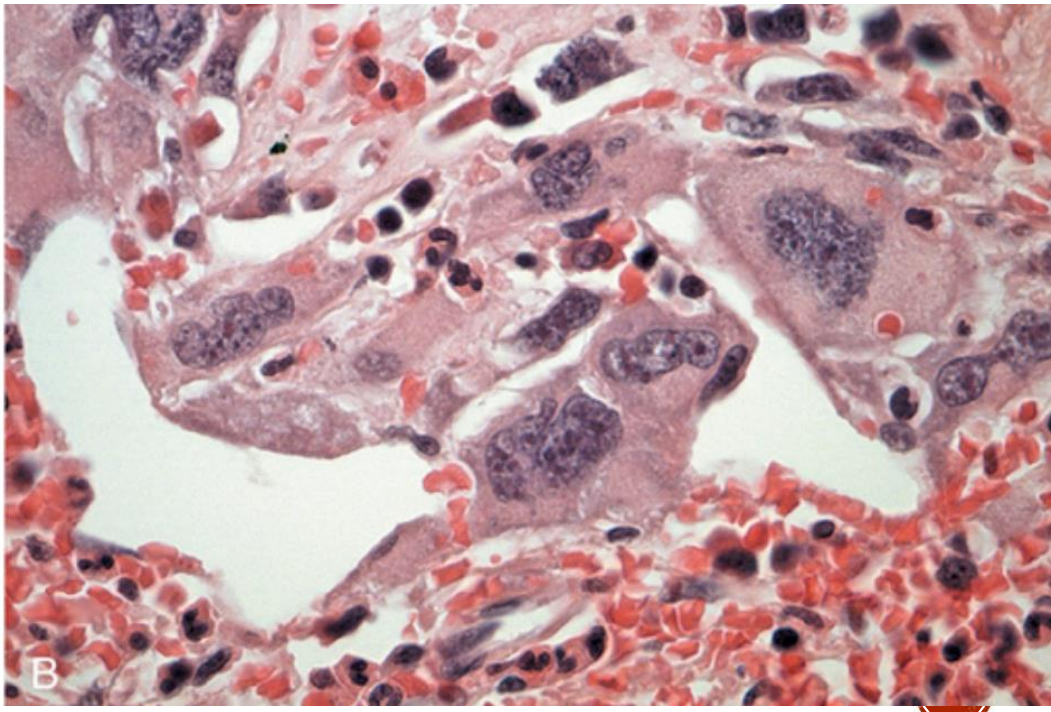
MORPHOLOGY

- 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





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

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

MYELODYSPLASTIC SYNDROME

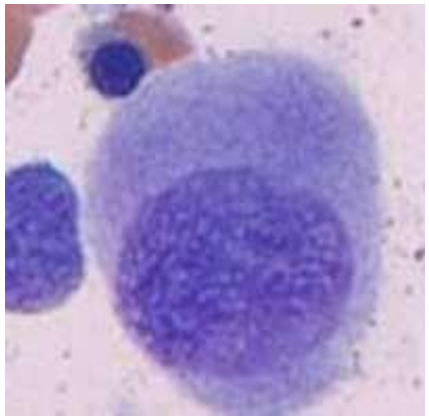
- Main feature is defective maturation, ineffective hematopoiesis, high risk for transformation to AML
- BM is replaced by a clonal progeny of transformed stem cell that has an capacity to differentiate into 3 cell lines but with abnormal morphology and function
- Hallmark of MDS: hypercellular BM, peripheral 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

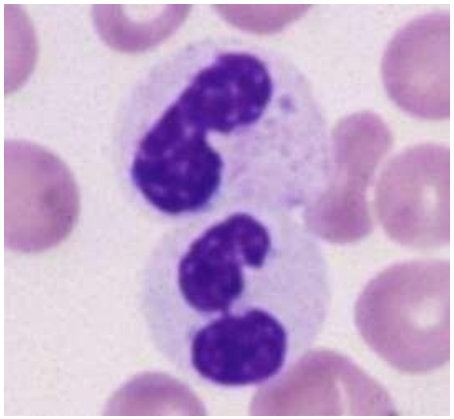
PATHOGENESIS

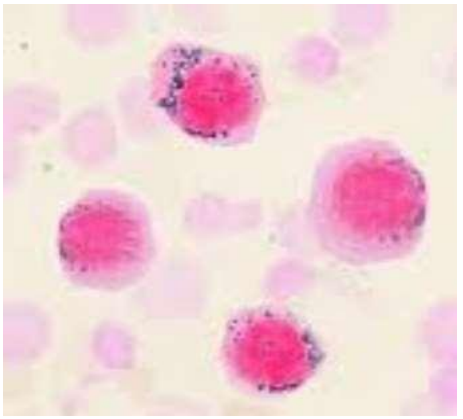
- Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8
- Mutations in epigenetic factors that regulate DNA methylation and histone modifications
- RNA splicing factors: abnormal RNA processing → ring sideroblasts
- Transcription factors
- 10% have P53 mutation

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







SYMPTOMS

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