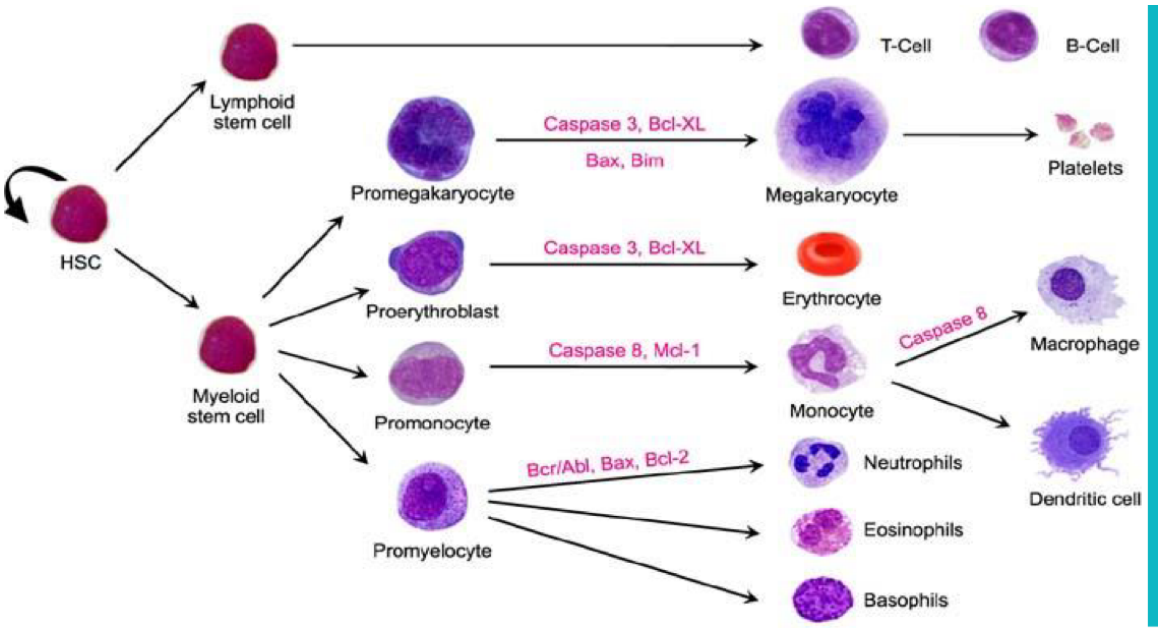


~ Myeloid Neoplasms

- Neoplasms originated from hematopoietic progenitors
- Primarily involve the bone marrow & replace normal marrow elements.
- Lesser secondary Hematopoietic organs involvement (LN , spleen & liver).

Acute myeloid leukemia (AML)

neoplastic cells are blocked at an early stage of development -> Immature myeloid cells (blasts) accumulate in BM & frequently circulate in PB.

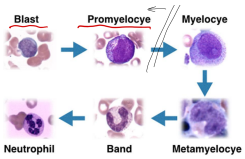
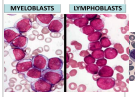
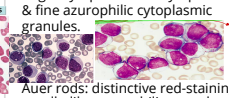
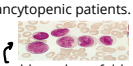
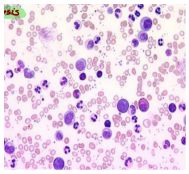
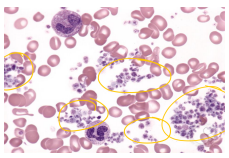
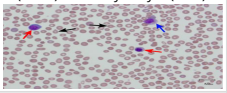
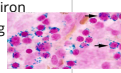
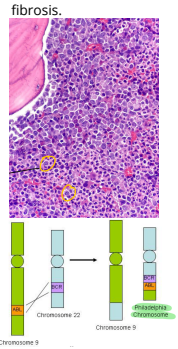
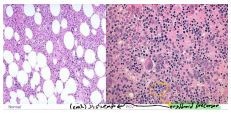
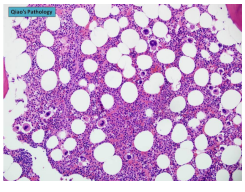
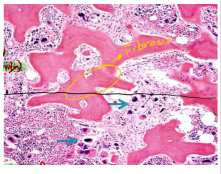
Myeloproliferative neoplasms (MPN):

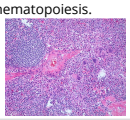
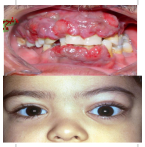
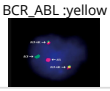
neoplastic clone continues to terminal differentiation but with increased or dysregulated growth.

- A group of disorders characterized by the presence of **mutated, constitutively activated tyrosine kinases** or other related molecules in signaling pathways → lead to growth factor independence.
- **Tyrosine kinase** Mutations do not impair differentiation.
- So the most common consequence is increase in production of one or more mature blood elements
- The neoplastic progenitors tend to seed secondary hematopoietic organs (spleen, liver, & LNs) → hepato-splenomegaly (**neoplastic** extramedullary hematopoiesis).
- MPNs often transform to AML

Myelodysplastic syndromes (MDS):

terminal differentiation occurs but in a disordered and ineffective fashion - dysplastic BM precursors & PB cytopenias.

	Acute myeloid leukemia (AML)	Chronic myeloid leukemia (CML)	Polycythemia vera (PCV)	Essential Thrombocythemia (ET)	Primary Myelofibrosis (PM)	Myelodysplastic Syndromes (MDS)
Mutation	▸ Most AMLs harbor mutations in genes encoding transcription factors that are required for normal myeloid cell differentiation interfere with the differentiation of early myeloid cells accumulation of myeloid precursors (blasts) in BM. 	characteristic BCR-ABL1 fusion gene produces a constitutively active BCR-ABL1 tyrosine kinase. presence of a chimeric BCR-ABL gene, derived from portions of the BCR gene on chr.22 & the ABL gene on chr.9 ▸ 95% of cases, the BCR-ABL gene is the product of a balanced t(9;22) translocation that moves ABL from chr.9 to a position on chr.22 adjacent to BCR. ▸ Translocation identified in some B-ALL.	The most common genetic abnormalities in "BCRABL–negative" MPNs are activating mutations in the tyrosine kinase JAK2. Strongly associated (> 97%) with activating point mutations in the tyrosine kinase JAK2.	▸ ET is associated with activating point mutations in JAK2 (50%), a receptor tyrosine kinase that is normally activated by thrombopoietin. ▸ Constitutive JAK2 renders the progenitor thrombopoietin-independent and leads to hyperproliferation.	▸ JAK2 mutations are present in 50% to 60% of cases ▸ Most of the remaining cases have other mutations which also give rise to increased JAK signaling.	▸ ~10% of MDS have loss-of-function mutations in tumor-suppressor gene TP53 often associated with chromosomal instability.
genatic	1)t(15;17) in acute promyelocytic Leukemia (APL) fusion of retinoic acid receptor α (RARA) gene on chr. 17 & PML gene on chr. 15 PML/RARA fusion protein blocks myeloid differentiation at promyelocytic stage. Favorable 2)(t[8;21], PML/RARA Favorable 3)inv[16]) CBFB/MYH11 Favorable	BCR-ABL : =constitutive signals generated decreased The growth factor dependence progenitors is greatly =mimic the effects of growth factor receptor activation. = does not inhibit differentiation, the early disease course is marked by excessive production of relatively normal blood cells =particularly granulocytes & platelets.	▸ JAK2 : normally acts in the signaling pathways downstream of the erythropoietin receptor. ▸ The most common JAK2 mutation lowers the dependence of hematopoietic cells on growth factors for growth and survival.	▸ The JAK2 mutation is the same as that found in almost all cases of PCV. ▸ Why some patients with JAK2 mutations present with PCV & others with ET not fully understood.	▸ Why JAK2 mutations are associated PCV in some patients & PM in others is not fully understood.	▸ Which is correlated with complex karyotype and poor clinical outcomes
Morphology Peripheral blood: 	** the presence of at least 20% myeloid blasts: have delicate nuclear chromatin, 2-4 nucleoli, larger cytoplasm than lymphoblasts & fine azurophilic cytoplasmic granules.  Auer rods: distinctive red-staining needle-like azurophilic granules, present in many cases. Numerous in acute promyelocytic leukemia (APL).  ▸ In other subtypes of AML, monoblasts, erythroblasts, or megakaryoblasts predominate. ▸ Occasionally, blasts are entirely absent from PB (aleukemic leukemia). ▸ For this reason, BM examination is essential to exclude acute leukemia in pancytopenic patients.  ▸ Monoblasts: have folded or lobulated nuclei, lack Auer rods.	▸ Leukocyte count is (often >100,000 cells/μL). ▸ Circulating cells are predominantly neutrophils, metamyelocytes & myelocytes. ▸ Basophils, eosinophils & platelets are increased 	*The major anatomic changes: increases in blood volume and viscosity -vascular stasis *Thromboses & infarctions are common *Hemoglobin levels Male: (Hb > 16,5 g/dl) Female: > 16 g/dl *Congestion of many tissues is characteristic. *Hepatomegaly & small foci of extramedullary hematopoiesis. *Platelets produced from the neoplastic clone often are dysfunctional elevated risk of thrombosis and bleeding Hemorrhages; often in GIT, oropharynx or brain. *often shows basophilia.	Peripheral smears usually reveal abnormally large platelets (large in size and in number)often accompanied by mild leukocytosis. 	PB smear is markedly abnormal Leukoerythroblastosis 1)Red cells often exhibit bizarre shapes (poikilocytes, teardrop cells) 2)Nucleated erythroid precursors. 3)Immature white cells (myelocytes and metamyelocytes). ▸ Along with abnormal large platelets . **PM - Morphology PB smear showing 2 nucleated RBCs (red), 2 tear drop RBCs (black) and a myelocyte (blue) 	**Dysplastic changes 1) Erythroid: Abnormal nuclear contour and iron deposits (ring sideroblasts) >50%  2) Myeloid: abnormal segmentation and granulation Pseudo-Pelger-Hüet cells, neutrophils with only two nuclear lobes  3) Megakaryocyte: single nuclear lobes or multiple separate nuclei (pawn ball megakaryocytes) 
Morphology BM:	promyelocytes of BM cellularity	▸ The bone marrow is hypercellular numbers of maturing granulocytic & megakaryocytic precursors. *Rarely progresses to spent phase with fibrosis. 	*is hypercellular owing to increased numbers of erythroid, myeloid, and megakaryocytic forms. *often progresses to a spent phase where the marrow is largely replaced by fibroblasts & collagen increase extramedullary hematopoiesis. 	cellularity is usually only mildly increased, but megakaryocytes are often markedly increased in number with abnormal large forms. 	+BM in advanced cases is hypocellular & diffusely fibrotic. + thickened bone (osteosclerosis) trabeculae(Branched)^ osteoblastic activity ^ + In early cases it may be hypercellular & only focal fibrosis. +(Abnormally large and clustered megakaryocytes,) very very specific 	BM is replaced by the clonal transformed multipotent stem cell that retains the capacity to differentiate into red cells, granulocytes, and platelets, but in an ineffective & disordered fashion. (cells stay in the BM) ▸ So; BM is hypercellular or normocellular, but the PB shows one or more cytopenias. ▸ The abnormal cells in BM are genetically unstable & prone to the acquisition of additional mutations transformation to AML.

Morphology Spleen	Splenomegaly & lymphadenopathy are less prominent than in ALL (Acute Lymphoblastic leukemia)	‣ Spleen resembles BM extensive extramedullary hematopoiesis. 	usually is slightly enlarged vascular congestion. Size in CML (due to seeding)larger than in pCV	//	//	//
Age	Affects all age group, peak > 60 years.	elderly Peaks in 4th & 5th decades.	elderly Insidious, usually in late middle age	elderly	‣ Age more than 60	Predominantly a disease of older adults, 70s
Clinical features: 	Clinical signs & symptoms; result from the replacement of normal marrow elements by leukemic blasts; symptoms related to anemia, thrombocytopenia, & neutropenia. ‣ Acute: present within a few weeks of the onset of symptoms. Patients present within weeks or a few months of the onset of symptoms. ‣ Symptoms of anemia, neutropenia, & thrombocytopenia, (fatigue, fever, and spontaneous mucosal & cutaneous bleeding). ‣ CNS manifestations are less frequent than ALL. ‣ Procoagulants and fibrinolytic factors released by leukemic cells, especially in AML with the t(15;17) high DIC incidence ‣ Tumors with monocytic differentiation often infiltrate the skin (leukemia cutis) & the gingiva. ‣ AML occasionally presents as a localized soft-tissue mass myeloblastoma or granulocytic sarcoma	‣ Initial symptoms usually are nonspecific (e.g., easy fatigability, weakness, weight loss). ‣ Sometimes the 1st symptom is a dragging sensation in the abdomen splenomegaly.	Most clinical signs & symptoms are related to an absolute increase in red cell mass. *Patients are plethoric & often cyanotic. *Pruritus Histamine released from the neoplastic basophils. *Thrombotic and hemorrhagic tendencies & hypertension. Headache, dizziness, GIT (hematemesis &melena) common. *erythromelalgia	*an indolent disorder with long asymptomatic periods only occasional thrombotic or hemorrhagic crises. *manifests clinically with elevated platelet counts also frequently demonstrate qualitative abnormalities in functional tests. *The types of thrombotic events resemble those observed in PCV. *A characteristic symptom erythromelalgia, a throbbing and burning of hands and feet caused by occlusion of small arterioles by platelet aggregates may also be seen in PCV.	The hallmark of primary myelofibrosis is the development of obliterative marrow fibrosis reduces bone marrow hematopoiesis 1) Cytopenias. 2) Extensive extramedullary hematopoiesis. ‣ Histologically, the appearance is identical to the spent phase that occurs occasionally late in the course of other MPN. ** ‣ Anemia and splenomegaly . ‣ Fatigue, weakness and night sweats ‣ Lab results; normochromic and normocytic anemia and Leukoerythroblatosis ‣ Bone marrow is essential for the diagnosis.	‣ Up to half of cases discovered incidentally. ‣ If symptomatic, it presents with weakness, infections, and hemorrhages all due to pancytopenia.
Diagnosis	//	Fluorescence in situ hybridization (FISH) for the BCR-ABL translocation BCR : green ABL : red BCR_ABL :yellow 	//	//	//	//
phases	//	1‣ Slowly progressive disease: Median survival is 3 years without treatment. 2‣ progress to accelerated phase: Anemia, new thrombocytopenia (additional genetic mutations). 3‣ Progress to blast phase: 70% AML 30% ALL Rarely progresses to spent phase with fibrosis.	//	//	//	//
Treatment	Treatment with all-trans retinoic acid (ATRA), an analogue of vitamin A, overcomes this block induce the neoplastic promyelocytes to differentiate into neutrophils rapidly clears the tumor.	‣ Tyrosine kinase inhibitors, like Imatinib *induces sustained remissions with manageable toxicity	Without treatment, death occurs from vascular complications within months..	//	‣ Treat with JAK2 inhibitors and HSCT.	//

	▸ The effect is very specific; AMLs without t(15;17) don't respond to ATRA. ▸ This is an important example of a	*prevents progression to blast crisis, particularly in patients with early disease (ap				
cell	//	particularly granulocytes & platelets. Specially Nutrophile	Excessive proliferation of erythroid, granulocytic, and megakaryocytic elements panmyelosis Specially RBc	Megakaryocyte proliferation** .with overproduction of platelets Elevated platelet counts* .(>600x10x9/L)	Bone marrow fibrosis	pancytopenia
prognosis	AML remains a devastating disease. ▸ Tumors with "good-risk" karyotypic abnormalities (t[8;21], inv[16]) are associated with a 50% chance of long- term disease-free survival. ▸ Overall survival in all patients is only 15-30% with conventional chemotherapy. ▸ t(15;17) AML have the best prognosis of any type curable in > 90%	//	▸ The median survival is increased to about 10 years by lowering the red cell count to near normal repeated phlebotomy. ▸ Prolonged survival a propensity to evolve to a "spent phase" (resembling PM) ~10 years. ▸ Extensive marrow fibrosis, hematopoiesis shifts to the spleen, which enlarges markedly.	▸ Median survival times 12~15years ▸ Transformation to myelofibrosis (spent phase)is uncommon. ▸ Transformation to acute leukemia is rare.	▸ Median survival is 4-5 years. ▸ 5-20% transform to AML. ▸ More difficult to treat than PCV and CML.	▸ Poor response to conventional chemotherapy. ▸ Transformation to AML in 10-40% (rapid in t-MDS) ▸ Prognosis is variable. ▸ Median survival time ranges from 9 to 29 months.
Pathogenesis	//	//	//	//	*Pathogenesis is similar between PM and spent phase MPN *The characteristic marrow fibrosis is caused by the inappropriate release of fibrogenic factors from neoplastic megakaryocytes. Two factors synthesized by megakaryocytes have been implicated (fibrogenic factors/fibroblast mitogens): 1)Platelet-derived growth factor (PDGF). 2)TGF-β. (collagen deposition and angiogenesis)	▸ A group of clonal stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis with cytopenias and a high risk of transformation to AML. Most cases are idiopathic, but some develop after exposure to carcinogens, previous cancer therapy, chemotherapy with alkylating agents or ionizing radiation therapy.
Immunophenotype	Immunologic markers are heterogeneous in AML. ▸ Most tumors express some combination of myeloid- associated antigens; CD13, CD14, CD15, or CD117 (KIT). ▸ CD34: a marker of hematopoietic stem cells & often present on myeloblasts. ▸ Myeloperoxidase (MPO) , most specific. ▸ Such markers are helpful in distinguishing AML from ALL and in identifying AMLs with only minimal differentiation.	//	//	//	//	
note	Risk factors Increase age. Male sex Previous cancer treatment. Exposure to radiation. (e.g., survivors of a nuclear reactor accident). Dangerous chemical exposure. (e.g., benzene)	Necessary to distinguish CML from a leukemoid reaction (infection, stress, chronic inflammation..) +Younger age, +No BCR/ABL fusion gene	Must be distinguished from: 1*relative polycythemia results from hemoconcentration(like dehydration) 2*absolute polycythemia is associated with high serum erythropoietin Neoplastic : PCV is associated with low serum erythropoietin	1) Separated from based on *PCV:the absence of polycythemia *primary myelofibrosis: the absence of marrow fibrosis 2) Causes of reactive thrombocytosis, (such as inflammatory disorders & iron deficiency) must be excluded	//	

Smoking; AML is linked to cigarette smoke (contains benzene & other

chemicals)

Other blood disorders (MDS, MPN)

Genetic disorders. (e.g., Down syndrome)

Classification

- AMLs are very diverse in terms of genetics, cellular lineage, and degree of maturation.
- WHO classification relies on all of these features to divide AML into four categories:

(1) AMLs ass with specific genetic aberrations: important coz they predict outcome & they guide therapy.

(2) AMLs with dysplasia: arise from MDSs.

(3) AMLs occurring after genotoxic chemotherapy.

(4) AMLs, Not otherwise specified: subclassified based on the

predominant line of differentiation

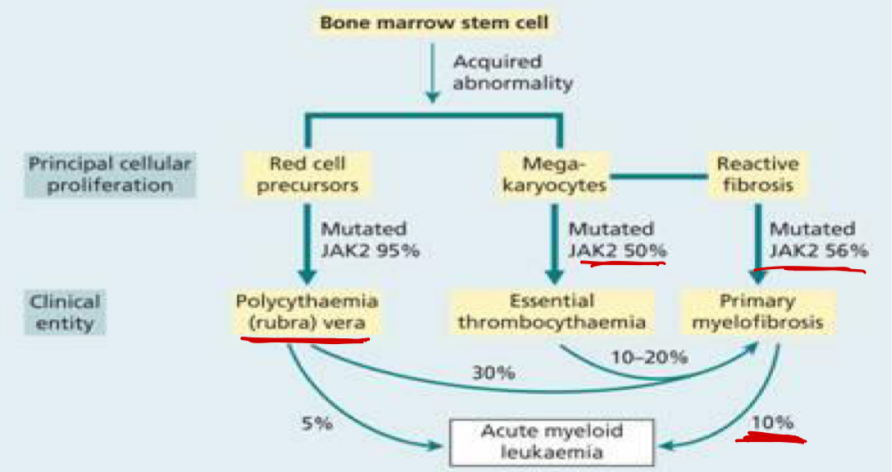
Acute vs Chronic leukemia

Acute leukemia	Chronic leukemia
Blasts	Mature cells
Rapid proliferation of cells.	Gradual proliferation.
Rapidly Fatal (<6 months without Tx)	More indolent disease. (3-6 years without Tx)
Lymphoid… ALL	Lymphoid… CLL
Myeloid… AML	MPN… CML

+Subsides with treatment of underlying infection

a reflection of growth factor–independent growth of the neoplastic clone.

before the diagnosis can be established



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