Subject: HLS - pathology

Topic: Lecture 10

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Myeloproliferative neoplasms		pathogenesis	Morphology	Clinical features
- maturation is normal, but proliferation is high - **active tyrosine kinase pathway independent of GFs** = BM is hypercellular + peripheral blood shows cytosis -causes **extramedullary hematopoiesis** -> hepatosplenomegaly - tend to transform into AML	**Chronic myeloid leukemia** (most common MPN) Affects adults 25-60 years Treatment: Imatinib [targeted treatment]	T(9;22) – Philadelphia gene -> fusion BCR/ABL gene -> **activation of tyrosine kinase** **[mutation is present in all BM cells especially myeloid cells]**	1-**leuckocyte count >100k** (mostly neutrophils) 2- **basophilia, eosinophilia** 3- **thrombocytosis** 4- **shift to left** (the presence of myelocyte and metamyelocyte in the blood) 5- **iron deficiency anemia** **BM: increased myeloid and megakaryocytes** **spleen: EMH** **blasts: low** it may be necessary to distinguish from a **leukemoid reaction** [high WBC and shift to left, occurs in severe inflammation/ may occur in CML]	1- Generally non-specific: fatigue, heavy abdomen, weight loss 2- it starts as **chronic disease** then the patient goes into an **accelerated phase** [worsening of symptoms, high WBC count, thrombocytopenia, resistance to imatinib] and a **blast phase/crisis** [transformation to acute leukemia (AML > ALL) + it can occur during the course of chronic disease without the accelerated phase]
	Polycythemia vera Usually in the late middle age Treatment: phlebotomy, JAK2 inhibitors	**Mutation in tyrosine kinase** JAK2 -> hematopoietic cells are less dependent on GFs and EPO -> excessive proliferation of erythroid, megakaryocyte and myeloid (***panmyelosis***) [Erythrocyte is the most prominent, low level of EPO] <-**to distinguish it from secondary polycythemia**	1-high RBC count (erythrocytosis) 2- leukocytosis is common including basophilia 3- thrombocytosis 4- hematocrit: above 60% 5- hemoglobin: above 18 g/dl for males and above 16 g/dl for female (polycythemia)	1-insidious onset of symptoms 2- plethora (skin full of erythema) 3- cyanosis 4- headache and dizziness (due to hypertension) 5- pruritis (secondary to activation of basophils) 6- peptic ulcers (due to secretion of histamines from basophils) 7- thrombosis and tissue infraction 8- GIT bleeding 9- Gout **Chronic phase** (after 10 years of symptoms) → **spent phase [bone marrow is fibrotic leading to more splenomegaly]** → **blast phase [rare]**
	Primary myelofibrosis Worst type Hallmark of this disease is ***fibrosis***	**JAK-STAT** signaling pathway is active in all cases. 50% have	**Peripheral blood: *tear-drop cells***, nucleated RBCs, shift to left **[leucoerythroblastic anemia]** **WBC:** can be normal or increased	1-over BM fibrosis, reducing capacity for hematopoiesis → cytopenia and massive EMH **Hypercellular -> hypocellular and fibrotic**

	+ RBC production is impaired+ patients have anemia Treatment: JAK2 inhibitors	mutation in JAK2, 5% in MPL gene. **Neoplastic megakaryocyte secretes TGF-B -> activates fibroblasts in BM to deposit reticulin and collagen + angiogenesis**	**Platelets:** high → low **BM:** (early) hypercellular and local fibrosis (late) hypocellular and extensive fibrosis ***Megakaryocyte*** DOMINANT CELLS	2- non-specific symptoms: weight loss, anemia, ***massive splenomegaly***, gout, bleeding, infection 3- worse outcome than CML and P vera. 4-5 years survival 4- frequent transformation to AML (5-20%)
	Essential thrombocythemia Best outcome and mildest disease.	**JAK2 mutation** is sometimes positive, but NO bone marrow fibrosis	Predominantly thrombocytosis and occasional leukocytosis	Splenomegaly is positive in 50%.

Langerhans Cell histiocytosis		
Neoplasm of dendritic cells (APCs)	**Multisystemic LCH**	**Unisystem LCH [eosinophilic granuloma]**
Langerhans cells express 2 markers: **CD1a and Langerin**	Occurs mostly in children (less than 2 years)	It affects **the bone** (most common and usually in children), then **skin, lung** (in old adults and usually smokers), and **stomach**.
Langerin is a transmembrane protein attached to Birbeck granules (have a tennis racket shape under EM) Proliferating Langerhans cells appear **large and vacuolated** similar to macrophages	Multiple cutaneous lesions composed of LCs Hepatosplenomegaly and lymphadenopathy Pulmonary lesions Osteolytic lesions Extensive bone marrow infiltration -> pancytopenia + myelophthisic anemia	Can be: **Unifocal** → commonly asymptomatic, can cause pain, **osteolytic lesions** **Multifocal** → presents in children, commonly affects calvaria bone, extends to pituitary gland causing **diabetes insipidus, exophthalmos** [Hand-Schuller-Christian triad] Proliferating LCs are admixed with numerous eosinophils, lymphocytes, plasma cells and neutrophils
Pathogenesis: acquired mutation in **serine/ threonine kinase BRAF**, leads to hyperactivity of this kinase	Treated with chemotherapy Survival is around 5 years	Treatment: Unifocal → surgical excision Multifocal → chemotherapy, sometimes spontaneous regression