PATHOPHYSIOLOGY OF HEMATOLOGIC MALIGNANCY

Disorder	Etiology and Epidemiology	Pathophysiology and Presentation	Lab Findings and Diagnosis	Treatment
		ACUTE LEUKEMIAS		
ACUTE MYELOGENOUS LEUKEMIA (AML)	Acquired chromosomal translocations or disjunctions **CBFα AML** : t(8; 21) Results in formation of CBFα-ETO fusion protein → transcriptional repressor of normal genes of differentiation (IL-3, GM-CSF, MCSF) **CBFβ AML** : inv(16) **Trisomy 8** and **t(9; 22)** are associated with poor prognosis **Incidence increases with age** Most cases occur > 50 yrs Gender disparity: more frequent in males Total risk is equivalent to solid tumor malignancy	**Blockade of differentiation** of cells in myeloid lineage before maturity and release from the bone marrow → **BONE MARROW REPLACEMENT** Pancytopenia Anemic symptoms, gram-negative sepsis, bleeding Bone pain **AND** → **INFILTRATION** Lymphadenopathy Splenomegaly CNS: meningeal and parenchymal dissemination, intracranial hemorrhage Pulmonary infiltrates Hepatic failure Renal failure Leukemia cutis Typical presentation in pancytopenic crisis DIC Tumor lysis syndrome (hypercalcemia, hyperkalemia) Febrile neutropenia Pulmonary failure (restrictive) Leukostasis (microvascualr ischemia resulting in retinopathy and hypoxia)	**PERIPHERAL SMEAR** Pancytopenia Circulating blast cells Cannot be differentiated from Lymphoblasts on inspection Auer rods within blast cell cytoplasm These are inclusions formed by myeloperoxidase granules **MARROW ASPIRATE** Blast proliferation (> 20% blasts) and hypercellularity **CYTOLOGIC ANALYSIS** Flow Cytometry: CD 13, CD 33 Indicates myeloid lineage IHC: myeloperoxidase stain is +ve FISH: t(8;21) No TCR or BCR rearrangements	**INTENSIVE CHEMOTHERAPY** Typically results in aplastic failure, thus transfuse with platelets and RBCs. **Febrile neutropenia** is treated empirically with broad-spectrum ABx (PMNs < 500/μL)
ACUTE PROMYELOCYTIC LEUKEMIA (APML)	Acquired chromosomal translocation **APML**: t(15;17) Results in apposition of the	**Blockade of differentiation** of cells and arrest as promyelocytes	**PERIPHERAL SMEAR** Pancytopenia Circulating promyelocytes	**Typically a more favorable prognosis**

	retinoid acid receptor and PML genes	**Associated with DIC** due to paraneoplastic secretion of TF by malignant cells Clinical presentation is similar to AML		**All-Trans Retinoic Acid (ATRA) Therapy** Allows normal differentiation to resume
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	**May arise from B-cell or T-cell lineages** **A pediatric disease** Median age at Dx is 13 yrs Ten-fold more common than AML in adults > 65 yrs	Clinical presentation is similar to AML	**CYTOLOGIC ANALYSIS** Flow Cytometry **B-cell**: CD19, CD22, CD10, TdT **T-cell**: CD3, CD7, CD2, CD5, TdT PCR: clonal immunoglobulin and TCR	**Typically better prognosis relative to AML**
MYELOPROLIFERATIVE DISORDERS				
CHRONIC MYELOGENOUS LEUKEMIA (CML)	Acquired chromosome translocation **Philidelphia chromosome**: t(9;22) Results in expression of a bcr-able fusion protein → constitutive tyrosine kinase activity and hyperproliferation → acquisition of additional mutations and progressive differentiation blockade **Ionizing radiation** **Benzene** Peak incidence in 25 – 60 yrs.	**Hyperproliferation of all myeloid lines** **Primarily involves the granulocytic lineage** **Chronic Phase:** ejection of granulocytic precursors at varying maturities (CBC similar to marrow differential) Leukocytosis Gout Massive splenomegaly Thrombocytosis Mild anemia Constitutional symptoms due to metabolic upregulation Anorexia, early satiety, abdominal pain due to **splenomegaly** **Blast Crisis:** progressive block in differentiation results in AML (70%) or ALL (30%)	**PERIPHERAL SMEAR** Basophilia Neutrophil precursors Thrombocytosis **Granulocytic precursor cells** representing spectrum of maturation	**Imatinib** Inhibits tyrosine kinase activity of bcr-abl In chronic phase, may perform allogenic stem cell transplant
POLYCYTEHMIA VERA	**JAK2 V617F** (seen universally) Results in constitutive activity	**EPO-independent erythropoeisis** Leads to increased Hct and viscosity	**Must R/O secondary etiologies of polycythemia**	**Phlebotomy** Reduce Hct < 45

	(autophosphorylation) of JAK2 without EPO binding to receptor	Headache, fatigue, visual changes, constitutional symotoms, pruritis with water contact **Thrombocytosis** Thrromboembolic events (mainly portal venous thrombosis) **Physical Findings** Splenomegaly, Plethora Hepatomegaly Systolic HTN **Increased risk of MF and AML**	Increase EPO: chronic lung disease, CO poisoning, shunts, high-affinity Hb, altitude Paraneoplastic syndrome: SCC, renal cell carcinoma, hepatic carcinoma **SERUM** Low EPO (typically elevated in secondary polycythemia) **MARROW ASPIRATE** Hyeprcellular with NML differentiation **CYTOLOGIC ANALYSIS** JAK2 V617F mutation	Resulting iron deficiency results in a hypoproliferative state, and is therapeutic **Low-dose aspirin** **Hydroxyurea** Decreases RBC and platelet production
ESSENTIAL THROMBOCYTOSIS	**JAK2 V617F** (50%) JAK2 is also involved in thrombopoeisis	**Increased proliferation of** megakaryocytes and increased platelet production Unregulated by TPO **Typically asymptomatic** (detect on CBC) **Thrombosis** **Bleeding Risk** **Splenomegaly**: more commonly seen in V617 variants **Erythromelalgia:** burning sensation in hands due to neuropathy **Increased risk of MF and AML**	**Must R/O secondary etiologies of thrombocytosis** Reactive (hemorrhage) Iron deficiency anemia Chonic inflammation Malignancy Recent splenectomy Bone Marrow Bx is NOT USEFUL Typically hypercellular with megakaryocyte hyperplasia **CYTOLOGIC ANALYSIS** JAK2 V617F mutation	**Hydroxyurea** Decreases platelet count **Low-dose aspirin** **Vigilance** in younger patients
PRIMARY MYELOFIBROSIS (MF) AGNOGENIC MYELOID	**JAK2 V617F** (50%) Other Myeloproliferative Disorders with increased mitotic activity in marrow	**Infiltration of marrow by fibroblasts** Can result from **any myeloproliferative disorder (secondary MF)**	**PERIPHERAL SMEAR** Anemia Thrombocytosis	**Allogenic bone marrow transplant**

METAPLASIA		Malignant stem cells and precursors → secrete FGF and PDGF → recruit fibroblasts → sclerosis and myelopthisis **Anemia** (nearly universal finding) **Pancytopenia** (less frequent, seen in late disease) **Extramedullary Hematopoeisis** **Massive Splenomegaly** **Early phase:** anemia + elevated WBC and platelets **Late phase:** pancytopenia	Nucleated erythroid precursors Neutrophil precursors Giant platelets Circulating megakaryocytes Dacrocytes **CYTOLOGIC ANALYSIS** JAK2 V617F mutation	**Splenectomy** **Hydroxyurea** (if thrombocytosis) **EPO** **Thalidomide** **Transufsion**
MYELODYSPLASTIC SYNDROMES				
MYELODYSPLASTIC SYNDROME (MDS)	**Ionizing Radiation** **ChemoRx** Thus: it is typically an iatrogenic disease Requires multiple mutations and genetic destabilization Aberrations in chromosomes 5 and 7 Median age 65 – 70 yrs	**Premature apoptosis of all precursors due to defective differentiation** Thus, the pathology is related to megaloblastic anemia due to folate deficiency **Ineffective Hematopoesis** Decreased output of terminally differentiated cells **Macrocytic Anemia** (nearly universal finding) **Pancytopenia** **Infection** **Bleedign Risk** **PROGRESSES TO AML** RF: blasts > 5% of marrow	**PERIPHERAL SMEAR** Macrocytic anemia Hypolobated and hypogranular neutrophils (pseudo Pelger-Huet) **MARROW ASPIRATE** Hypercellular marrow with many aberrancies Small hypolobated megakaryocytes Megaloblastic change in erythroid precursors Ringed sideroblasts Increased blast population	**Loss of Chomosome 7** is associated with greater malignancy Favorable prognosis is associated with **loss of Chromosome 5** from tumor cell clones

LYMPHOMAS

HODGKIN LYMPHOMA (HL)	**De-differentiation of B-cells** Results in the malignant **Reed-Sternberg cell.** **Classic HL :** four subtypes (e.g. nodular sclerosing HL) **Nodular Lymphocyte-Predominant HL:** associated with good prognosis **Associated with EBV** **Bimodal distribution of incidence:** peaks at 20 – 40 and > 60 yrs	NaïveB-cell → germinal reaction → recombination → malignant transformation → RS cell No secretion of functional immunoglobulin Loss of normal B-cell CD markers Expression of CD 30 Secretion of cytokines and chemotactic signals **Painless lymphadenopathy** Most common presentation **Cough (with mediastinal nodal mass)** **B-symptoms** Fever, night sweats, weight loss **Pruritis** **Normocytic anemia** **Immune Dysfunction** Generally **depression CMI** due to secretion of inhibitory cytokines **Cutaneous anergy (**no DTH) **Decreased T lymphocyte count** **Susceptibility** to viral and fungal infection (immunoglobin synthesis is not affected)	**LYMPH NODE Bx** **RS cells are diagnostic of HL** Large binucleated cells with prominent nucleoli **Inflammatory Infiltrate** RS cells are surrounded by an inflammatory stroma (eosinophils, small lymphocytes, plasma cells) **May demonstrate fibrosis** **PERIPHERAL SMEAR** Normocytic anemia Lymphopenia **SERUM** Increased ESR Increased LDH **STAGING** Whole body CT Bone Marrow Bx PET scan I: Isolated lymphadenopthy II: Multiple positive nodes ipsilateral to diaphragm III: Spread across diaphragm IV: Disseminated disease affected non-lymphoid tissues A: no constitutional symptoms B: constitutional symptoms	Remission is achieved in 70 – 80% of cases **Priority** is staging I and II: short-course chemoradiation III and IV: fractionated chemoradiation
NON-HODGKIN LYMPHOMA (NHL)	Chromosomal translocations during maturation in germinal center	CLINICAL PRESENTATION IS SIMILAR TO HL	**STAGING** Has less weight in prognosis relative to HL	**Indolent** Typically, therapy is initiated only when disease becomes

	80% are B-cell lymphomas May also develop from T and NK cells **Follicular Lymphoma :** t(14; 18) Results in apposition of the IgH promoter with *bcl-2* Thus, indolent course **Diffuse Large Cell Lymphoma :** t(3; 18) **Burkitt Lymphoma :** t(8; 14) Results in apposition of IgH promoter with *c-myc* Thus, high grade lymphoma **Risk Factors** Immunosuppression (e.g. PTLD) Chronic infection: EBV, HepC, *H. pylori* This results in increased antigen presentation and clonal selection of B-cells within germinal center reactions	**Indolent Lymphoma:** slow growth but refractory to treatment. Cells are relatively differentiated. **High grade lymphoma:** rapid growth and sensitive to treatment. Cells are anaplastic. **Extranodal disease**: bone and GI tract **Immune Dysfunction** This is due to aberrant expression of immunoglobulin Autoimmune hemolytic anemia (typically warm hemolysis) Immunoglobulin deficiency Monoclonal gammopathy Susceptible to bacterial infection	β2-microglobulin (prognostic in indolent lymphoma) LDH (prognostic in high-grade disease) Whole body CT PET scan CSF analysis (if high-grade subtype is suspected) **RFs for increased mortality** Age > 60 yrs PS > 1 Increased LDH Involvement of extralypmhatic sites (dissemination) Stages III or IV	symptomatic **High-grade lymphoma** *R-CHOP therapy* Rituximab Cyclophosphamide Vincritine Prednisone *XRT* Typically for palliation of local symptoms **Peds:** requires intensive treatment with agents targeting the CNS
CHRONIC LYMPHOCYTIC LEUKEMIA SMALL LYMPHOCYTIC LYMPHOMA	Most common adult leukemia > 40 yrs: malignancy is leading cause of lymophocytosis	**Typically asymptomatic and Dx with unexplained leukocytosis** **Immunodeficiency** Decreased synthesis of functional immunoglobulin Depressed CMI: cutaneous anergy due to secretion of inhibitory cytokines and soluble co-stimulatory receptors **Autoimmune Disease** Autoimmune Hemolytic Anemia ITP **Pancytopenia** Most mortality is due to infection	**PERIPHERAL SMEAR** Abundance of small well-differentiated lymphocytes (> 5k/μL) Smudged cells **CYTOLOGIC ANALYSIS** **Flow Cytometry** Monoclonal B-cells: **CD19, CD5**, CD20, CD23 Skewed κ:λ ratio (NML is 3:1) PCR: clonal immunoglobulin and TCR	**Asymptomatic:** typically no treatment

		Malignant transformation to Diffuse Large B-cell Lymphoma		
NON-MALIGNANT LYMPHATIC PROCESSES				
REACTIVE FOLLICULAR HYPERPLASIA	Lymphoctysis secondary to infection < 40 yrs: infection is leading cause of lymphocytosis **EBV** **Pertussis**	**Infectious Mononucleosis** (EBV) Fever, pharyngitis, lymphadenopathy, rash, splenomegaly, hepatomegaly, hepatitis	**PERIPHERAL SMEAR** Atypical reactive lymphocytes (expanded cytoplasm with extension abutting RBCs) These are CD8+ T-cells in EBV **Anemia is rare!** Monospot assay : detects heterophile Abs IgM against viral capsid and early antigen PCR Lymph nodes typically demonstrate heterogenous B-cells within germinal centers + macrophages	
PLASMA CELL NEOPLASM				
MULTIPLE MYELOMA	**Malignant transformation of plasma cells** Primary mutagenic event is IgH : oncogene translocation **Risk Factors:** radiation, pesticides FH, MGUS, osseous plasmocytoma Nearly all incidence occurs among age > 40 yrs Second leading hematologic malignancy	**Initial presentation:** weakness, fatigue, back pain, infections, renal disease **Marrow Failure due to Replacement** Pancytopenia Plasmacytoma: extramedullary extensions of primary plasma cell tumors Cord compression **Hyperglobulinemia** Due to secretion and circulation of M protein Hyperviscosity syndrome Renal tubular injury Platelet and coagulative dysfunction	**PERIPHERAL SMEAR** Plasma cell leukemia (rare) Rouleaux formation Pancytopenia (usually) **SERUM** Hyperproteinemia Hypercalcemia Increased ESR (aggregation of RBCs) Increased viscosity SPEP: M spike, globally depressed immunoglobulin signal In light chain myeloma, no M spike is seen UPEP: monoclonal light chain (in all	**Chemoradiation** **Bisphosphonates** (reverse bone disease and remove serum calcium) **Manage pain** **Renal protection** **Autologous stem cell transplant** **Allogenic bone marroe transplant**

	60% monoclonal IgG 20% monoclonal IgA < 20% free light chain Non-secretory Polyclonal IgD and IgE: very rare IgM: most likely WM	Amyloidosis Peripheral neuropathy **Bone Disease** Bone pain Lytic bone lesions : due to secretion of RANKL (activate osteoclasts) and DKK-1 (inhibits osteobalst differentiation) Pathologic fracture Hypercalcemia **Immune Deficiency** Disrupted AMI due to dysregulation of Ig production and normal humoral response	secretory MM; **Bence-Jones Protein**), albumin (with nephrotic syndrome) This is not seen on the SPEP **MARROW ASPIRATE** Hyperproliferation of plasma cells (> 5%) **Plasmacytoma** (may be extramedullary or osseous) Deposition of amyloid **CYTOLOGIC ANALYSIS** Skewed expression of κ:λ IgH (14q23) translocation **Dx REQUIRES:** M protein in SPEP or UPEP > 10% plasma cells in marrow Plasmacytoma Extramedullary infiltration: hypercalcemia, renal disease, bone lysis Anemia	
WALDENSTROM MACROGLOBULINEMIA	**Malignancy involving lymphoplasmocytic lymphocytes** These are partially differentiated plasma cells with some characteristics of B cells This is considered an **indolent NHL**	**Some common features with MM** Infiltrates bone marrow and causes aplasia (anemia is more common) Platelet and coagulative dysfunction Results bleeding risk Peak incidence occurs with age > 60 yrs Peripheral neuropathy **Some distinguishing features (from MM)** Lymphadenophy (B-cell receptors allow for residence in nodes) **Low-grade subtype of NHL**	**PERIPHERAL SMEAR** Anemia Pancytopenia (occasional) Rouleaux formation Visible agglutination Positive cold-agglutinin test Positive cryoglobulin **SERUM** Hyperproteinemia SPEP: M spike in gamma region **MARROW ASPIRATE or LYMPH NODE**	**Tx only if symptomatic** Rituximab Plasmapheresis (removes IgM) This is usually not therapeutic in MM since the M protein in IgG (primarily interstitial)

		Hyperviscosity Syndrome is common Venous insufficiency CNS: lethargy, headache, visual changes, coma, stroke CHF due to increased ECV Cold AutoimmuneHemolytic Anemia Cryoglobulinemia No lytic bone disease Renal disease is uncommon **Transformation to Diffuse Large B-cell Lymphoma** Similar to CLL	**Bx** Lymphoplasmacytic monoclonal B cells **Dx REQUIRES:** Serum monoclonal IgM Lymphoplasmacytic B cells in bone marrow or lymph nodes	
AMYLOIDOSIS	**Extracellular deposition of amyloid protein** AL (light chain): typically seen in λ chain myeloma or aberrant light chain secretion Derived from processing by macrophages AA (secondary): resulting from chronic inflammation Most patients: MGUS with M-spike; 20% with MM	Cardiomegaly **Restrictive Cardiomyopathy** Hepatomegaly Splenomegaly Carpal Tunnel Syndrome Peripheral Neuropathy **Nephrotic Syndrome** Macroglossia Periorbital Purpura GI malabsoption and bleeding	**Dx** Requires LM (under polarized light) of tissue Bx	**Tx** is similar to MM
MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)	**Detection of M protein in serum** without underlying malignancy > 70 yrs: incidence is 5%	**No significant pathology** **Increased risk of MM, WM, and amlyoidosis** Approximately 1% per yr and 25 – 40% overall risk from time of Dx **Depressed polyclonal immunoglobulin**	**Dx REQUIRES:** M protein < 3 g/dL Plasma cells < 10% of bone marrow No lytic bone disease No tissue involvement r/o NHL and amyloidosis	