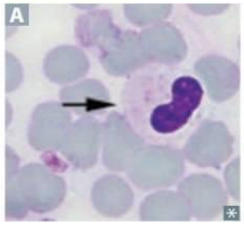
Patho (MPN I - II & MDS)
Lec (12 + 10)

Myelodysplastic syndromes



Stem cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Bone marrow blasts <20% (vs >20% in AML). Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

Pseudo-Pelger-Huët anomaly—neutrophils with bilobed ("duet") nuclei A. Associated with myelodysplastic syndromes or drugs (eg, immunosuppressants).

Erythroid: Abnormal nuclear abnormalities & iron deposits (ring sideroblasts)

Megakaryocyte: single nuclear lobes or multiple separate nuclei (pawn ball megakaryocytes)

Myeloproliferative neoplasms

Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

Polycythemia vera

Primary polycythemia. Disorder of ↑ RBCs, usually due to acquired *JAK2* mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A.

↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

Essential thrombocythemia

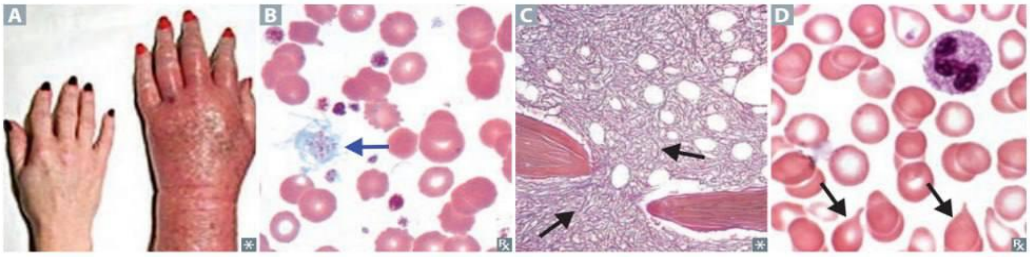
Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed B. Erythromelalgia may occur.

Myelofibrosis

Atypical megakaryocyte hyperplasia → ↑ TGF-β secretion → ↑ fibroblast activity → obliteration of bone marrow with fibrosis C. Associated with massive splenomegaly and "teardrop" RBCs D.

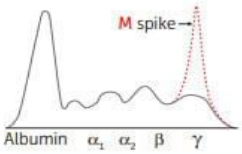
"Bone marrow cries because it's fibrosed and is a dry tap." leukoerythroblastosis

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	*JAK2* MUTATIONS
Polycythemia vera	↑	↑	↑	⊖	⊕
Essential thrombocythemia	–	–	↑	⊖	⊕ (30–50%)
Myelofibrosis	↓	Variable	Variable	⊖	⊕ (30–50%)
CML	↓	↑	↑	⊕	⊖



Patho 8 (Plasma Cell Neoplasms)

Plasma cell dyscrasias



Characterized by monoclonal immunoglobulin (paraprotein) overproduction due to plasma cell disorder.

Labs: serum protein electrophoresis (SPEP) or free light chain (FLC) assay for initial tests (M spike on SPEP represents overproduction of a monoclonal Ig fragment). For urinalysis, use 24-hr urine protein electrophoresis (UPEP) to detect light chain, as routine urine dipstick detects only albumin.

Confirm with bone marrow biopsy.

Multiple myeloma

Overproduction of IgG (55% of cases) > IgA.

Clinical features: CRAB

- HyperCalcemia
- Renal involvement
- Anemia
- Bone lytic lesions ("punched out" on X-ray A) → back pain.

Peripheral blood smear shows rouleaux formation B (RBCs stacked like poker chips).

Urinalysis shows Ig light chains (Bence Jones proteinuria) with ⊖ urine dipstick.

Bone marrow analysis shows > 10% monoclonal plasma cells with clock-face chromatin C and intracytoplasmic inclusions containing IgG.

Complications: ↑ infection risk, 1° amyloidosis (AL).

Waldenstrom macroglobulinemia

Overproduction of IgM (macroglobulinemia because IgM is the largest Ig).

Clinical features:

- Peripheral neuropathy
- No CRAB findings
- Hyperviscosity syndrome:
  - Headache
  - Blurry vision
  - Raynaud phenomenon
  - Retinal hemorrhages

Bone marrow analysis shows >10% small lymphocytes with intranuclear pseudoinclusions containing IgM (lymphoplasmacytic lymphoma).

Complication: thrombosis.

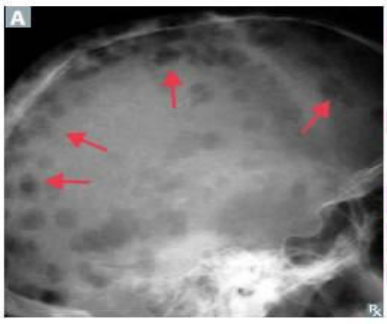
Monoclonal gammopathy of undetermined significance

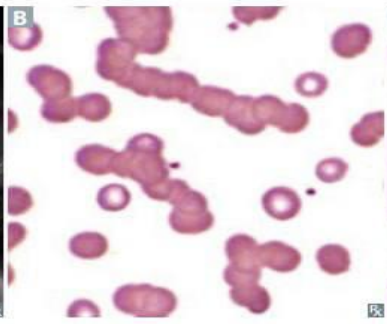
Overproduction of any Ig type.

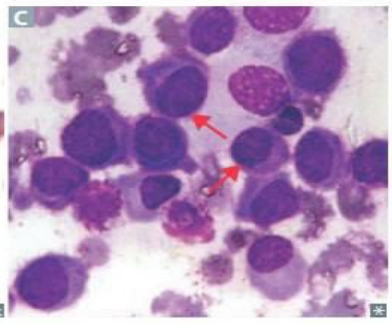
Usually asymptomatic. No CRAB findings.

Bone marrow analysis shows < 10% monoclonal plasma cells.

Complication: 1-2% risk per year of transitioning to multiple myeloma.





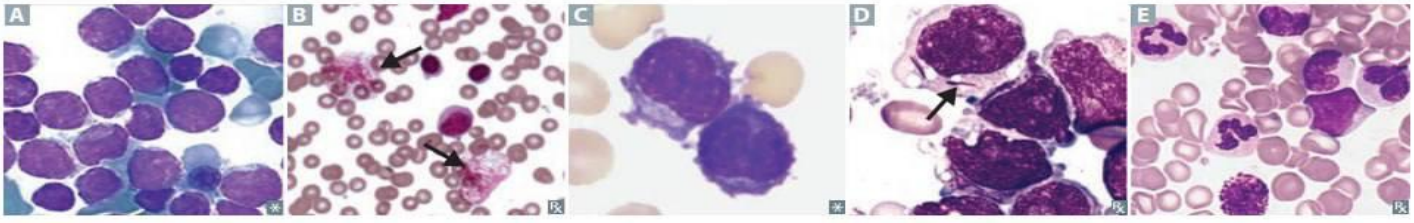


Patho (leukemia I & II)
Lec (7 + 5)

Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood), although some cases present with normal/↓ WBCs.
Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

TYPE	NOTES
Lymphoid neoplasms	
Acute lymphoblastic leukemia/lymphoma	Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis; t(9;22) (Philadelphia chromosome) → worse prognosis.
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Age > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. CLL = Crushed Little Lymphocytes (smudge cells). Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).
Hairy cell leukemia	Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon. Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia. Stains TRAP (Tartrate-Resistant Acid Phosphatase) ⊕ (TRAPped in a hairy situation). TRAP stain largely replaced with flow cytometry. Associated with *BRAF* mutations. Treatment: purine analogs (cladribine, pentostatin).
Myeloid neoplasms	
Acute myelogenous leukemia	Median onset 65 years. Auer rods D; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear. Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]). APL: t(15;17), responds to all-*trans* retinoic acid (vitamin A) and arsenic trioxide, which induce differentiation of promyelocytes; DIC is a common presentation.
Chronic myelogenous leukemia	Peak incidence: 45—85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], *BCR-ABL*) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL ("blast crisis"). Responds to BCR-ABL tyrosine kinase inhibitors (eg, imatinib).

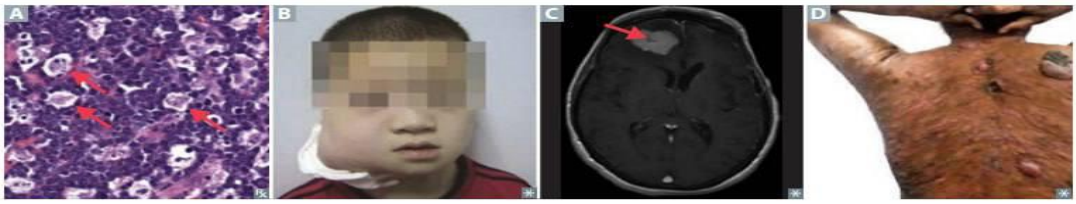


Patho (lymphoma I & II)
Lec (6 + 11)

Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER
t(8;14)	Burkitt (Burk-8) lymphoma (c-*myc* activation)
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)
t(11;18)	Marginal zone lymphoma
t(14;18)	Follicular lymphoma (*BCL*-2 activation)
t(15;17)	APL (formerly M3 type of AML)
t(9;22) (Philadelphia chromosome)	CML (*BCR-ABL* hybrid), ALL (less common); Philadelphia CreaML cheese

			lymphoma; may regress with *H pylori* eradication]).
Primary central nervous system lymphoma	Adults	EBV related; associated with HIV/AIDS	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients C, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
Neoplasms of mature T cells			
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug use)	Adults present with cutaneous lesions; common in Japan (T-cell in Tokyo), West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.
Mycosis fungoides/ Sézary syndrome	Adults		Mycosis fungoides: skin patches and plaques D (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with "cerebriform" nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia).



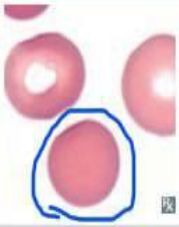
Lymphoma	Discrete tumor mass arising from lymph nodes. Variable clinical presentation (eg, arising in atypical sites, leukemic presentation).

Hodgkin vs non-Hodgkin lymphoma	Hodgkin	Non-Hodgkin
	Both may present with constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss.	
	Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis.
	Characterized by Reed-Sternberg cells.	Majority involve B cells; a few are of T-cell lineage.
	Bimodal distribution: young adulthood and > 55 years; more common in males except for nodular sclerosing type.	Can occur in children and adults.
	Associated with EBV.	May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

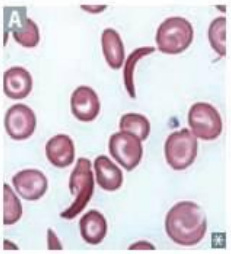
Patho

Patho . Lec3
Hemolytic anemia

RBC morphology *(continued)*

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Spherocytes		Hereditary spherocytosis, autoimmune hemolytic anemia	Small, spherical cells without central pallor ↓ surface area-to-volume ratio
Macro-ovalocytes		Megaloblastic anemia (also hypersegmented PMNs)	
Target cells		HbC disease, Asplenia, Liver disease, Thalassemia	"HALT," said the hunter to his target ↑ surface area-to-volume ratio
Sickle cells		Sickle cell anemia	Sickling occurs with low O_2 conditions (eg, high altitude, acidosis)

Intrinsic hemolytic anemias

	DESCRIPTION	FINDINGS
Hereditary spherocytosis	Primarily autosomal dominant. Due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin). Small, round RBCs with less surface area and no central pallor (↑ MCHC) → premature removal by spleen (extravascular hemolysis).	Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 infection). Labs: ↓ mean fluorescence of RBCs in eosin 5-maleimide (EMA) binding test, ↑ fragility in osmotic fragility test. Normal to ↓ MCV with abundance of RBCs. Treatment: splenectomy.
G6PD deficiency	X-linked recessive. G6PD defect → ↓ NADPH → ↓ reduced glutathione → ↑ RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, fava beans) → hemolysis. Causes extravascular and intravascular hemolysis.	Back pain, hemoglobinuria a few days after oxidant stress. Labs: blood smear shows RBCs with Heinz bodies and bite cells. "Stress makes me eat bites of fava beans with Heinz ketchup."
Pyruvate kinase deficiency	Autosomal recessive. Pyruvate kinase defect → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG → ↓ hemoglobin affinity for O_2.	Hemolytic anemia in a newborn. Labs: blood smear shows burr cells.
Paroxysmal nocturnal hemoglobinuria	Hematopoietic stem cell mutation → ↑ complement-mediated intravascular hemolysis, especially at night. Acquired *PIGA* mutation → impaired GPI anchor synthesis for decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59), which protect RBC membrane from complement.	Triad: Coombs ⊖ hemolytic anemia, pancytopenia, venous thrombosis (eg, Budd-Chiari syndrome). Pink/red urine in morning. Associated with aplastic anemia, acute leukemias. Labs: CD55/59 ⊖ RBCs on flow cytometry. Treatment: eculizumab (targets terminal complement protein C5).
Sickle cell anemia  A	Point mutation in β-globin gene → single amino acid substitution (glutamic acid → valine). Mutant HbA is termed HbS. Causes extravascular and intravascular hemolysis. Pathogenesis: low O_2, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia, vaso-occlusive disease. Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS. Heterozygotes (sickle cell trait) have resistance to malaria. Most common autosomal recessive disease in Black population. Sickle cells are crescent-shaped RBCs A. "Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias).	Complications in sickle cell disease: ▪ Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19). ▪ Autosplenectomy (Howell-Jolly bodies) → ↑ risk of infection by encapsulated organisms (eg, *S pneumoniae*). ▪ Splenic infarct/sequestration crisis. ▪ *Salmonella* osteomyelitis. ▪ Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke. ▪ Sickling in renal medulla (↓ Po_2) → renal papillary necrosis → hematuria. Hb electrophoresis: ↓↓ HbA, ↑ HbF, ↑↑ HbS. Treatment: hydroxyurea (↑ HbF), hydration.

Interpretation of iron studies

	Iron deficiency	Chronic disease
Serum iron	↓	↓
Transferrin or TIBC	↑	↓[a]
Ferritin	↓	↑
% transferrin saturation (serum iron/TIBC)	↓↓	—/↓

↑↓ = 1° disturbance.

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.