📚 HEMATOLOGY AND ONCOLOGY FOR USMLE 📚

Myelodysplastic Syndromes (MDS) & Myeloproliferative Neoplasms (MPNs)

These are clonal hematopoietic stem cell disorders, but they differ fundamentally:

- MDS → ineffective production (cytopenias)
- MPNs → excessive production (cytoses)

Think of them as opposite ends of the myeloid spectrum ⚖️

🔬 MYELODYSPLASTIC SYNDROMES (MDS)

🧠 Definition

Clonal stem cell disorders characterized by:

- Ineffective hematopoiesis
- Dysplastic maturation of non-lymphoid cells

- Bone marrow blasts < 20%
- Risk of transformation to AML

More common in older adults 👴🏻

🧬 Etiology

De novo mutations (most common)

OR

Environmental exposure:

- Radiation ☢️
- Benzene 🧪
- Chemotherapy

These cause genomic instability in hematopoietic stem cells.

🔁 Pathophysiology

Stem cell mutation → Abnormal myeloid maturation → Ineffective hematopoiesis → Increased apoptosis in marrow → Cytopenias (anemia, neutropenia, thrombocytopenia)

If mutation burden increases → Blasts rise → ≥ 20% blasts → Transformation to AML 🔥

🔬 Pseudo-Pelger-Huët Anomaly

Neutrophils with:

- Bilobed nuclei ("duet" nuclei) 🎵
- Hyposegmented appearance

Seen in:

- MDS
- Certain drugs (immunosuppressants)

📌 High-yield morphology clue.

📊 MDS vs AML

Feature	MDS	AML
Blasts	< 20%	≥ 20%
Onset	Gradual	Acute
Marrow	Dysplastic	Packed with blasts
Risk	May progress	Already malignant

🔬 MYELOPROLIFERATIVE NEOPLASMS (MPNs)

These are malignant clonal disorders with increased production of mature myeloid cells.

Unlike MDS, these have overproduction rather than failure.

🟥 Polycythemia Vera (PV)

🧬 Genetics

Acquired JAK2 mutation (very high yield)

JAK2 mutation → Constitutive tyrosine kinase activation → Cytokine-independent erythropoiesis → Increased RBC production

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🔁 Mechanism Flowchart

JAK2 mutation → Constant activation of JAK-STAT pathway → Increased RBC production → Hyperviscosity → Thrombosis risk

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🩺 Clinical Features

- Aquagenic pruritus (itching after hot shower) 🚿
- Erythromelalgia (burning red-blue extremities) 🔥
- Thrombosis (DVT, PE, Budd-Chiari)

- Hyperviscosity symptoms

📌 EPO levels ↓ (distinguishes from secondary polycythemia)

💊 Treatment

- Phlebotomy
- Hydroxyurea
- Ruxolitinib (JAK1/2 inhibitor)

2️⃣ Essential Thrombocythemia (ET)

🧬 Genetics

- Often JAK2 mutation (30–50%)

🧠 Pathophysiology

Megakaryocyte proliferation → Massive platelet production → Thrombosis + bleeding

Why bleeding?
Platelets may be dysfunctional.

🩺 Features

- Very high platelet count
- Large, abnormal platelets on smear
- Erythromelalgia may occur

3️⃣ Primary Myelofibrosis

🧠 Pathophysiology

Atypical megakaryocyte hyperplasia → Increased TGF-β secretion → Fibroblast activation → Bone marrow fibrosis → Marrow failure

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🔁 Splenomegaly

Megakaryocyte proliferation → TGF-β release →
Fibroblast activation → Bone marrow fibrosis →
Extramedullary hematopoiesis → Massive splenomegaly

🔬 Classic Findings

- "Teardrop" RBCs 💧
- Dry tap on bone marrow aspiration
- Massive splenomegaly

📌 "Bone marrow cries because it's fibrosed."

📊 MPN Comparison Table

Disease	RBCs	WBCs	Platelets	Philadelphia Chromosome	JAK2
Polycythemia vera	↑	↑	↑	–	+
Essential thrombo cythemia	–	–	↑	–	+ (30–50%)
Myelofibrosis	↓	Variable	Variable	–	+ (30–50%)
CML	↓	↑	↑	–	+

4️⃣ Chronic Myelogenous Leukemia (CML)

🧬 Genetics

- Philadelphia chromosome
- t(9;22)
- BCR-ABL fusion protein
- Constitutive tyrosine kinase activation

🔁 Mechanism

BCR-ABL → Constant proliferative signaling → Excess myeloid cells → Marked leukocytosis

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🔬 Leukemoid Reaction vs CML

Feature	Leukemoid Reaction	CML
Definition	Reactive neutrophilia (>50,000)	Myeloproliferative neoplasm
BCR-ABL	–	+

Neutrophils	Toxic granulation, Döhle bodies	Pseudo-Pelger-Huët
LAP score	↑	↓
Eosinophils/ Basophils	Normal	Increased

📌 Exam Trick:

Low LAP score = CML

High LAP score = Leukemoid reaction

🎯 Exam Points

- Aquagenic pruritus = Polycythemia vera
- EPO ↓ = PV (primary cause)
- Teardrop RBCs + massive spleen = Myelofibrosis
- BCR-ABL = CML
- LAP low = CML

- Bilobed neutrophils = MDS
- Blasts ≥20% = AML

🧠 Big Picture Comparison

MDS → defective maturation → cytopenias

MPN → excessive proliferation → cytoses

If the exam shows:

Elderly + cytopenias + dysplastic cells → MDS

If the exam shows:

Elevated counts + JAK2 or BCR-ABL mutation → MPN

🔴 POLYCYTHEMIA

Polycythemia = increased hemoglobin/hematocrit.

But the mechanism differs

📊 Classification Table

Type	Plasma Volume	RBC Mass	O_2 Sat.	EPO Level	Associations
Relative	↓	–	–	–	Dehydration, burns
Appropriate Absolute	–	↑	↓	↑	Lung disease, congenital heart disease, high altitude, OSA
Inappropriate Absolute	–	↑	–	↑	Exogenous EPO, androgen use, RCC, HCC
Polycythemia Vera (PV)	–	↑ ↑	–	↓	JAK2 mutation

📌 Key idea:

Absolute polycythemia = ↑ RBC mass

Relative polycythemia = ↓ plasma volume

🔁 Mechanism Flowcharts

🟠 Relative Polycythemia

Fluid loss → ↓ Plasma volume → Hemoconcentration → ↑ Hematocrit (false increase)

🟢 Appropriate Absolute Polycythemia

Hypoxia (lung disease, high altitude) → Kidney senses ↓ O_2 → ↑ EPO production → ↑ RBC mass

📌 O_2 saturation ↓

📌 EPO ↑

🔵 Inappropriate Absolute Polycythemia

Normal oxygen levels → Tumor or drug secretes EPO → ↑ RBC mass

Common causes:

- Renal cell carcinoma (RCC)
- Hepatocellular carcinoma (HCC)
- Exogenous EPO (athletes "blood doping" 🏃)

📌 O_2 normal

📌 EPO elevated

🔴 Polycythemia Vera (Primary)

JAK2 mutation → Constitutive JAK-STAT activation → Erythropoiesis independent of EPO → ↑ ↑ RBC mass

Negative feedback → Suppressed renal EPO production → ↓ EPO levels

📌 High-yield distinction:
PV = RBC ↑ + EPO ↓

🧬 Chromosomal Translocations

📊 Translocation Summary Table

Translocation	Disorder	Key Gene Effect
t(8;14)	Burkitt lymphoma	c-MYC activation
t(11;14)	Mantle cell lymphoma	Cyclin D1 activation
t(11;18)	Marginal zone lymphoma	MALT pathway
t(14;18)	Follicular lymphoma	BCL-2 activation
t(15;17)	Acute promyelocytic leukemia (APL)	PML-RARA fusion
t(9;22)	CML (± ALL)	BCR-ABL

🧠 Why Ig Heavy Chain Is Important

Chromosome 14 contains Ig heavy chain genes, which are constantly active in B cells.

If oncogenes (c-MYC, BCL-2, Cyclin D1) get translocated next to chromosome 14:

Ig heavy chain promoter → Continuous gene expression → Oncogene overexpression → Malignant proliferation ⚡

🦴 Langerhans Cell Histiocytosis (LCH)

🔬 Definition

A proliferative disorder of Langerhans cells (antigen-presenting dendritic cells normally in skin).

🩺 Classic Presentation

Child with:

- Lytic bone lesions
- Skin rash
- Recurrent otitis media

- Mastoid bone mass

🧠 Pathophysiology

Abnormal Langerhans cell proliferation → Functionally immature cells → Poor T-cell stimulation → Tissue infiltration

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🧪 Key Markers

- S-100 positive
- CD1a positive
- Birbeck granules on EM

Birbeck granules:

- Rod-shaped
- "Tennis racket" appearance 🎾
- Very classic exam clue.

💥 Tumor Lysis Syndrome (TLS)

An oncologic emergency ⚠️

Occurs after rapid tumor cell destruction (often lymphomas/leukemias).

Can happen:

- After chemotherapy
- Spontaneously in fast-growing cancers

🔁 Pathophysiology Flowchart

Massive tumor cell lysis → Release of intracellular contents

→ ↑ Potassium
→ ↑ Phosphate
→ ↑ Nucleic acids

Nucleic acids → Broken down into uric acid → Hyperuricemia

Phosphate binds calcium → ↓ Calcium (hypocalcemia)

Resulting in:

- Arrhythmias ⚡
- Seizures
- Tetany
- Acute kidney injury

🧪 Laboratory Pattern

Electrolyte	Change
K^+	↑
PO_4^{3-}	↑
Uric acid	↑
Ca^{2+}	↓

🩺 Complications

- ECG changes
- Muscle weakness
- Calcium phosphate crystals in kidney
- Uric acid crystals
- Acute renal failure

💊 Prevention & Treatment

High-risk patient → Aggressive IV hydration

Prevention:

- Allopurinol (inhibits xanthine oxidase)
- Rasburicase (breaks down uric acid)

📌 Rasburicase works faster → used in high-risk patients.

🎯 Exam Points

- RBC ↑ + EPO ↓ = Polycythemia vera
- RBC ↑ + EPO ↑ + hypoxia = Appropriate secondary polycythemia
- t(15;17) = APL → treat with ATRA
- Birbeck granules = Langerhans cell histiocytosis
- Hyperkalemia + hyperphosphatemia + hypocalcemia after chemo = Tumor lysis syndrome

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-> The End <-