Myeloproliferative Neoplasms (MPNs)

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Learning Objectives

- Recognize common clinical presentations of the classic MPNs and CML
- Understand core molecular pathogenesis (JAK–STAT activation; BCR::ABL1 tyrosine kinase)
- Apply stepwise diagnostic algorithms for erythrocytosis, thrombocytosis, leukocytosis, and splenomegaly
- Outline first-line and advanced therapies, including TKIs and JAK inhibitors

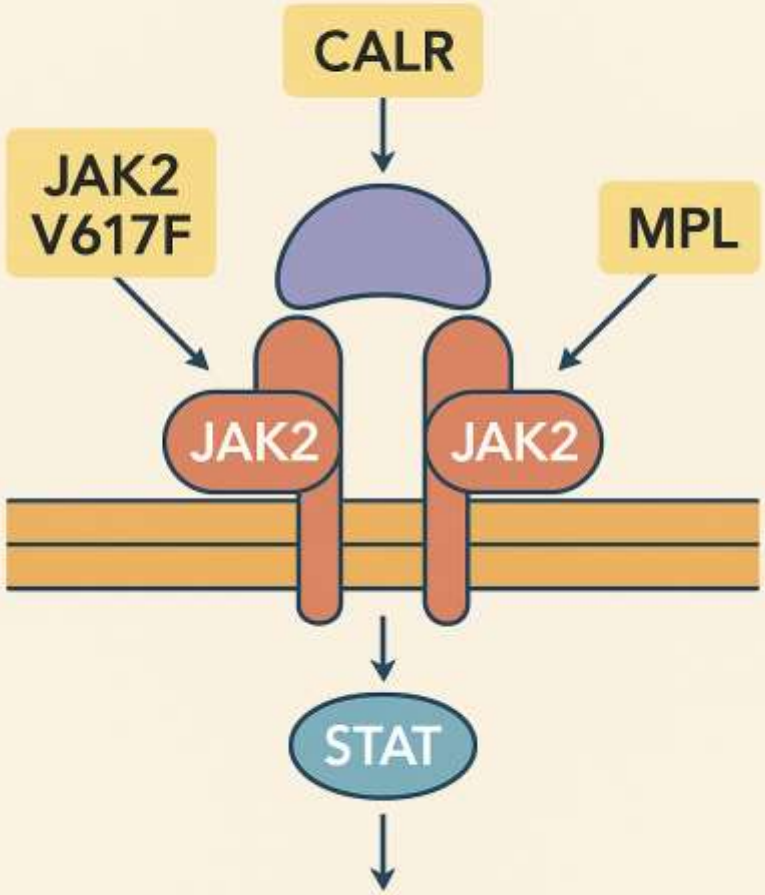
MPN Landscape & Classification

- Clonal hematopoietic stem cell disorders with overproduction of mature myeloid cells
- Classic BCR::ABL1-negative MPNs: Essential Thrombocythemia (ET), Polycythemia Vera (PV), Primary Myelofibrosis (PMF)
- BCR::ABL1-positive MPN: Chronic Myeloid Leukemia (CML)
- Driver mutations: JAK2, CALR, MPL (ET/PMF); JAK2 in nearly all PV; BCR::ABL1 in CML
- Natural history: thrombohemorrhagic events, splenomegaly, constitutional symptoms; risk of progression to MF or AML

Driver Mutations in Myeloproliferative Neoplasms (MPNs)

Myeloproliferative neoplasms (MPNs) — which include **polycythemia vera (PV)**, **essential thrombocythemia (ET)**, and **primary myelofibrosis (PMF)** — are clonal disorders of hematopoietic stem cells characterized by uncontrolled proliferation of one or more myeloid lineages. Their pathogenesis revolves around a small set of **driver mutations** that lead to **constitutive activation of the JAK-STAT signaling pathway**, promoting cytokine-independent growth and survival of myeloid cells.

Driver Mutations in Myeloproliferative Neoplasms (MPNs)



1. JAK2 Mutations

- JAK2 V617F

- **Most common driver mutation** in MPNs.
- Found in:
  - ~95% of **Polycythemia Vera (PV)**
  - ~50–60% of **ET** and **PMF**
- **Mechanism:**
  - A point mutation in exon 14 of the **JAK2** gene substitutes valine (V) for phenylalanine (F) at position 617.
  - This mutation **activates JAK2 kinase** constitutively — even in the absence of cytokine binding.
  - Downstream effect: continuous activation of **STAT**, **MAPK**, and **PI3K** pathways → proliferation and survival of myeloid cells.

- JAK2 Exon 12 Mutations

- Seen in ~2–3% of **PV** cases that are **JAK2 V617F–negative**.
- Typically cause **erythrocytosis** without marked leukocytosis or thrombocytosis.
- Lead to isolated activation of the erythropoietin receptor signaling.

2. CALR (Calreticulin) Mutations

- Occur in **JAK2- and MPL-negative ET or PMF** (~20–35% of such cases).
- Usually **frameshift mutations** in exon 9, producing a novel C-terminal peptide.
- **Mechanism:**
  - Mutant CALR binds to **MPL (thrombopoietin receptor)** on the cell surface.
  - Causes **constitutive activation of JAK-STAT signaling** through MPL.
- **Clinical implications:**
  - CALR-mutated ET/PMF tends to have:
    - **Higher platelet counts**
    - **Lower thrombotic risk** than JAK2-mutated cases
    - **Better overall prognosis**

3. MPL (Myeloproliferative Leukemia Virus Oncogene) Mutations

- Found in ~3–5% of **ET** and **PMF**.
- Common variants: **MPL W515L/K**
- **Mechanism:**
  - Mutation leads to **ligand-independent activation** of the **thrombopoietin receptor**.
  - Activates JAK2 downstream signaling → megakaryocytic and platelet proliferation.

Clinical Presentations — Across MPNs

- Constitutional: fatigue, night sweats, weight loss, low-grade fevers
- Vascular: arterial/venous thrombosis, microvascular symptoms (headache, erythromelalgia, visual changes)
- Organomegaly: splenomegaly (early satiety, LUQ pain), hepatomegaly
- Hemorrhagic risk (especially with extreme thrombocytosis and acquired vWF disease)
- Pruritus (aquagenic in PV), gout/hyperuricemia, bone pain

Essential Thrombocythemia (ET) — Definition & Epidemiology

- **Definition**
  - Sustained thrombocytosis due to clonal megakaryocytic proliferation
  - Median age ~60; female predominance; incidental discovery common
  - Thrombotic and hemorrhagic complications drive morbidity

ET — Pathophysiology

- Driver mutations: JAK2 V617F (~50–60%), CALR (~20–30%), MPL (~5–10%), triple-negative (~10%)
- Megakaryocyte hyperplasia with large hyperlobulated forms
- Platelet activation and inflammatory cytokines contribute to events

ET — Presentation

- Often asymptomatic thrombocytosis; microvascular symptoms (headache, dizziness, erythromelalgia)
- Thrombosis: arterial (TIA/stroke, MI) and venous (DVT/PE, splanchnic)
- Bleeding with extreme counts (>1,000 ×10^9/L) due to acquired vWF deficiency
- Mild splenomegaly

ET — Diagnosis (Approach)

- Confirm sustained platelet count ≥450 ×10^9/L on repeat CBCs
- Exclude secondary/reactive causes: iron deficiency, inflammation, infection, malignancy, postsplenectomy, drugs
- Molecular testing: JAK2/CALR/MPL; "triple-negative" supports clonal disease if morphology fits
- Bone marrow: megakaryocytic proliferation with large hyperlobulated forms; minimal granulocytic/erythroid increase
- Rule out PV, CML, and PMF (early) by labs, morphology, and molecular studies

ET — Risk Stratification & Treatment

- Risk of thrombosis: age ≥60, prior thrombosis, JAK2 mutation (intermediate effect)
- Low risk (age <60, no thrombosis): low-dose aspirin if no bleeding risk
- High risk (≥60 or prior thrombosis): cytoreduction (hydroxyurea first-line; peg-IFN as alternative), plus aspirin
- Extreme thrombocytosis with bleeding: avoid ASA; correct acquired vWF; consider cytoreduction
- Pregnancy: favor interferon-α; avoid hydroxyurea; manage aspirin carefully

Polycythemia Vera (PV) — Definition & Epidemiology

- **Definition**
  - Clonal erythrocytosis with panmyelosis; nearly all with JAK2 V617F or exon 12 mutation
  - Median age ~60; pruritus, plethora; high thrombotic risk

PV — Pathophysiology

- Constitutive JAK2 activation → erythropoietin-independent erythropoiesis
- Low serum EPO; leukocytosis and thrombocytosis common
- Iron deficiency from phlebotomy can mask erythrocytosis (microcytosis, ↑RDW)

PV — Presentation

- Aquagenic pruritus, facial plethora, erythromelalgia, headache, dizziness
- Thrombosis: stroke/TIA, MI; atypical sites (Budd–Chiari, portal vein)
- Gout, peptic symptoms; splenomegaly; hypertension

PV — Diagnosis (Approach)

- Elevated Hb/Hct (approx. Hb >16 g/dL women, >16.5 g/dL men; or Hct >48% women, >49% men) — use local ref
- Low EPO level supports PV
- Molecular: JAK2 V617F or exon 12; bone marrow panmyelosis
- Exclude secondary erythrocytosis (hypoxia, smoking/CO, OSA, high altitude, renal lesions, exogenous EPO)
- Masked PV: microcytosis and normal Hb/Hct due to iron deficiency; rely on RBC mass or marrow/molecular

PV — Treatment

- All: low-dose aspirin (unless bleeding risk) and phlebotomy to Hct target ≤45%
- High-risk (age ≥60 or prior thrombosis): add cytoreduction (hydroxyurea first-line; peg-IFN an alternative)
- Ruxolitinib for HU-intolerant/resistant PV (control Hct/symptoms, reduce spleen size)
- Manage CV risk factors; treat pruritus (antihistamines, SSRIs, JAK inhibitors)

Primary Myelofibrosis (PMF) — Definition & Epidemiology

- **Definition**
  - Clonal MPN with marrow fibrosis, ineffective hematopoiesis, and extramedullary hematopoiesis
  - Median age ~65–70; symptomatic splenomegaly and constitutional symptoms are common
  - Can be primary or evolve from ET/PV (post-ET/PV MF)

PMF — Pathophysiology

- Driver: JAK2 (~50–60%), CALR (~25–30%), MPL (~5–10%); others influence prognosis (ASXL1, SRSF2, U2AF1, IDH1/2, EZH2)
- Cytokine-mediated fibroblast activation → reticulin/collagen fibrosis
- Leukoerythroblastosis and extramedullary hematopoiesis (spleen/liver)

PMF — Presentation

- Fatigue, night sweats, weight loss; severe splenomegaly with early satiety/abdominal pain
- Anemia, variable platelets/WBC; bone pain
- Cachexia; constitutional symptom burden high

PMF — Diagnosis (Approach)

- Peripheral blood: anemia, tear-drop RBCs, nucleated RBCs, leukoerythroblastosis
- Bone marrow: hypercellular early → fibrotic later; reticulin/collagen grading; atypical megakaryocytes
- Exclude CML, PV, ET, MDS, and reactive fibrosis; confirm driver mutation or clonal markers
- Risk models: DIPSS/DIPSS-plus; MIPSS70/MIPSS70-plus v2.0; GIPSS (genetic-only)

Chronic Myeloid Leukemia (CML) — Definition & Phases

- **Definition**
  - BCR::ABL1-positive MPN with uncontrolled granulocytic proliferation
  - Phases: chronic phase (CP) → accelerated phase (AP) → blast crisis (BC)
  - Most present in CP with leukocytosis, basophilia, and splenomegaly

CML — Pathophysiology

- BCR::ABL1 fusion protein: constitutive tyrosine kinase activity → downstream PI3K/AKT, RAS/MAPK, JAK/STAT
- Philadelphia chromosome t(9;22)(q34;q11); p210 most common (e13a2/e14a2 transcripts)
- Tyrosine kinase inhibitors (TKIs) target ATP-binding site; resistance via kinase domain mutations or amplification

CML — Presentation

- Fatigue, weight loss, night sweats, abdominal fullness (splenomegaly)
- CBC: marked leukocytosis with left shift; basophilia; thrombocytosis or thrombocytopenia
- Hyperuricemia; Gout

CML — Diagnosis (Approach)

- Confirm BCR::ABL1 by RT-qPCR (IS), FISH, or karyotype; exclude BCR::ABL1-negative MPNs
- Assess phase (CP/AP/BC) based on blasts, basophils, platelets, cytogenetics
- Baseline risk scores

CML — Treatment & Monitoring

- First-line TKIs: imatinib, dasatinib, nilotinib, bosutinib; special cases: asciminib after ≥2 TKIs or intolerance
- Response milestones (IS % BCR::ABL1): ≤10% at 3 months, ≤1% at 6 months, ≤0.1% (MMR) at 12 months
- Failure/resistance → assess adherence, drug interactions; perform mutation analysis; switch TKI accordingly
- Treatment-free remission (TFR) possible after sustained deep response (MR4/4.5) with close monitoring

Approach to Erythrocytosis

- Confirm persistent elevation; check Hct/Hb vs sex-specific thresholds
- Serum EPO: low suggests PV; normal/high suggests secondary
- Assess O2 saturation, smoking/CO level, OSA, renal/hepatic imaging, and exogenous androgens/EPO
- JAK2 testing if PV suspected; marrow in ambiguous cases

Approach to Thrombocytosis

- Repeat CBC & smear; iron studies (ferritin/TSAT), CRP; look for infection/inflammation, malignancy
- If persistent and no secondary cause → JAK2/CALR/MPL testing
- Bone marrow to distinguish ET from prefibrotic MF and other myeloid neoplasms

Approach to Leukocytosis & Splenomegaly

- Differentiate leukemoid reaction vs clonal process: infection/inflammation workup
- Consider CML with basophilia and marked left shift → BCR::ABL1 testing
- Ultrasound/CT for spleen size; correlate with symptoms

Complications & Disease Progression

- Arterial/venous thrombosis and hemorrhage (ET/PV)
- Evolution to secondary myelofibrosis (post-ET/PV MF)
- Blast transformation to AML (risk highest in MF, then PV/ET)
- Pregnancy considerations and periprocedural management

Supportive Care & Special Situations

- Antithrombotic management: ASA, AC after thrombosis (balance bleeding risk)
- Managing pruritus (PV), gout, and iron deficiency
- Peri-operative management: control counts; hold ASA based on bleeding risk
- Fertility/pregnancy: prefer interferon; avoid hydroxyurea and most TKIs (consult guidelines)

Case 1 — 58-year-old with Platelets 980 ×10^9/L

Presentation

Symptoms: headaches, burning feet; no bleeding

Labs: Hb 13.8, WBC 9.5; ferritin normal

JAK2 V617F positive; marrow: large hyperlobulated megakaryocytes

Interpretation & Plan

Dx: Essential thrombocythemia

Tx: ASA. cytoreduction (HU) due to age ≥60

Counsel re: thrombosis risk

Case 2 — 45-year-old lady with Hct 55%

Key Points

Symptoms: pruritus; splenomegaly
Labs: low EPO; JAK2 V617F positive
Marrow: panmyelosis

Interpretation & Plan

Dx: Polycythemia vera
Tx: Phlebotomy to Hct ≤45% + ASA;
Control CV risks

Case 3 — 39-year-old with WBC 120 ×10^9/L and Basophilia

Key Points

Symptoms: fatigue, early satiety; spleen palpable
FISH: BCR::ABL1 positive; PCR IS 45%
Karyotype: t(9;22)

Interpretation & Plan

Dx: Chronic phase CML
Tx: Start TKI (e.g., imatinib/dasatinib/nilotinib)
Monitor PCR at 3, 6, 12 months to meet milestones