Myeloproliferative Neoplasms

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Objectives

• Overview of MPN
• New WHO 2016 criteria
• Practical diagnostic strategies
• Diagnostic traps
Myeloproliferative Neoplasms (WHO 2016)

- CML, \textit{BCR-ABL1} +
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia (CEL)
- MPN, unclassifiable
CML

• 1st genetically defined leukemia

• Must document *BCR-ABL1* fusion gene for diagnosis
CML: basophilia, blast, neuts predominate
BM: hypolobated megas; Bld: ↑↑ WBC
Hx: 32-year-old female with splenomegaly

CBC: WBC 24,300, Hgb 8.4, Hct 28%, Plt 701,000

BM: Dry tap

Cytog: t(9;22)(q34.1;q11.2)

Imatinib: limited response
10% blasts, 20% basos, anemia
Blast, baso, mega fragment, anemia
Bone Marrow Core Biopsy

Hypercellular, fibrosis
Bone Marrow Core Biopsy

Sheets, hypolobated megakaryocytes
Dx: CML: Accelerated Phase

- Increase in blasts (10-19%)
- Cytopenias/dysplasia
- Increase in basophils ($\geq 20\%$)
- Additional cytogenetic abnormalities
- Imatinib resistance
CML in Blast Phase

• ≥ 20% myeloid lineage blasts (80% of cases)

• Lymphoid blast phase (20% of cases) (Usually) precursor B

• Focus of blast effacement in BM, extramedullary site
Exemplary Case:

- 28-yr-old male with fatigue and back pain

- **CBC:**
  - WBC: 215.4
  - H/H: 9.7/27
  - MCV: 87
  - Plt: 97
Blood

Marked leukocytosis; cytopenias
Blood

Basophilia, left shift, non-toxic
Flow cytometry of Blood
Blood Key Features

- Striking neutrophilia (ANC 130.0)
- Basophilia (ABC 9.0)
- Eosinophilia (AEC 16.5)
- Left shift (Blast 2%); myeloblasts by flow cytometry
- Anemia, thrombocytopenia

BM: Dry tap
Differential Dx

• MDS/MPN
• MPN-not likely stable phase
• Specific MPN: CML, CNL, ?CEL
Dry tap: Touch prep

Variably sized immature cells
Increased immature cells
Flow Cytometry Disaggregated Bone Marrow
Karyotype Primary Clone

1 2 3 4 5
6 7 8 9 10
11 12 13 14 15
16 17 18 19 20
21 22 X
Karyotype Secondary Clone
Genetic Studies of BM

Cytogenetics:
47, XY, +8, t(9;22) [17], idem, + der 22t(9;22) [3]
Clonal evolution with second t(9;22)

Molecular:
Q BCR-ABL1 positive with transcript ratio of 0.55 c/w CML at diagnosis
Dx: CML presenting in B-lymphoid blast phase in BM; clonal evolution by CC (double Philadelphia chromosome) (5% of CML patients present in AP or Blast Phase)
Myeloproliferative Neoplasms

Diagnosis **requires** integration of

- **Clinical** (e.g. spleen size)
- **Hematologic** (sequential CBC data)
- **Other laboratory data** (e.g. LDH)
- **Morphologic** (blood and bone marrow)
- **Genetic features** (*BCR-ABL1, JAK2, CALR, MPL, CSF-3R*)

Disorders are characterized by

- **Uncontrolled cell proliferation** (usually multiple lineages)
- **Intact maturation** (mature cells predominate)
JAK2, MPL, and CALR Mutations in Philadelphia – Negative MPN

Source: Klampfl, et al. NEJM 2013; 369: 2379
Impact of Mutations on Dx and Outcome

• PV - Virtually always has JAK2 or Exon 12 mutation
• ET - best outcome for triple negative
• PMF - best outcome for CALR mutation (many types)
• CNL - virtually all cases have CSF-3R mutation
Asymptomatic Patient

74 yr-old female
Hgb 17; Hct 51%
Plt 950,000

Erythrocytosis, thrombocytosis
74 yr-old female
Hgb 17; Hct 51%
Plt 950,000

BM aspirate: ↑ cell, ↑ megakaryocytes
74 yr-old female
Hgb 17; Hct 51%
Plt 950,000

BM aspirate: all lineages; quant, qual
74 yr-old female
Hgb 17; Hct 51%
Plt 950,000

Cellularity, bone Δ, sinuses
74 yr-old female
Hgb 17; Hct 51%
Plt 950,000

BM biopsy: ↑ megs, dilated sinuses, EMH
Key Considerations

• Unexplained erythrocytosis and thrombocytosis
• Hypercellular BM with intact maturation
• Dilated sinuses
• Abnormal megakaryocytes
  - Hyperlobated, clustered
  - Dilated sinuses with megakaryocytes
• Genetic testing- $JAK2^+$

Dx: PV
Polycythemia Vera (PV) 2016: Key Tips

• Megakaryocyte morphology and $JAK2$ mutation positivity added to major criteria along with panmyelosis

• Only subnormal serum EPO level retained as minor criteria
Polycythemia Vera (PV) 2016:

**Major Criteria:**

1) Elevated Hgb/Hct
   a. $\geq 16.5/49\%$ Men
   b. $\geq 16/48\%$ Women

2) Megakaryocyte morphology, panmyelosis

3) $JAK2$ V617F or $JAK2$ Exon 12 mutation

**Minor Criterion:**

- Subnormal serum EPO level

**Dx:** All 3 major OR 1st 2 major plus minor
MEGAKARYOCYTES KEY IN MPN

CML

PV

PMF

ET
Essential Thrombocythemia

BM: hyperlobulated megas; Bld: ↑↑ plts

1.7 million plts
**Essential Thrombocythemia (ET) 2016:**

**Major Criteria:**

1) Sustained thrombocytosis $\geq 450 \times 10^9/L$

2)Distinctive megakaryocyte morphology; Lacks granulocytic or erythroid lineage expansion in BM

3) Exclusionary criteria (exclude CML, PV, PMF, MDS, other)

4) Presence of $JAK2$, $CALR$, or $MPL$ mutation

**Minor Criteria:**

- Another clonal marker
- Absence of evidence for reactive thrombocytosis

**Dx:** All 4 major OR 1st 3 major plus 1 minor
Primary Myelofibrosis

BM: pleomorphic megakaryocytes; Bld: LER
Primary Myelofibrosis

Marked osteosclerosis
Primary Myelofibrosis (PMF) 2016:

**Major Criteria:**

1) Megakaryocyte morphology, granulocytic lineage expansion

2) Not meeting criteria for CML, PV, MDS, other myeloid neoplasm

3) $JAK2$ or $CALR$ or $MPL$ mutation

   OR

   Presence of another clonal marker OR absence of evidence for reactive reticulin fibrosis

**Minor Criteria:**

a. Anemia  
d. Increased LDH

b. Leukocytosis  
c. Splenomegaly (palpable)

Dx: All 3 major plus $\geq 1$ minor for prefibrotic
Primary Myelofibrosis Fibrotic Stage

**Major Criteria:**
- Megakaryocyte proliferation, atypia and reticulin/collagen fibrosis grades 2 or 3
- Exclusions: ET, PV, CML, MDS, other myeloid neoplasm
- JAK2, CALR or MPL mutation
  - OR
    - Another clonal marker
  - OR
    - Exclusion of reactive myelofibrosis

**Minor Criteria:**
- a. Anemia
- b. Leukocytosis
- c. Splenomegaly (palpable)
- d. Increased LDH
- e. LER

Dx: All 3 major plus ≥ 1 minor criteria
Exemplary Case

53-yr-old female

CBC: WBC 2,300, RBC 3.3, Hgb 9.3, Hct 27%, Plt 121,000
Pancytopenia

NRBC’S, no blasts
Bone marrow core: osteosclerosis
Bone marrow core, CD34
Bone marrow core, reticulin
• Pancytopenia
• Prominent bone changes, fibrosis, enlarged megakaryocytes
• MDS, MDS/MPN, MPN in advanced phase
• Clinical information required
  • Long hx of PV
  • Marked splenomegaly

• Additional tests required
  • $BCR-ABL1 (-)$
  • $JAK2 (+)$
  • CC if possible
Diagnosis

Postpolycythememic myelofibrosis

**Key data:** hx of PV

$JAK2^+$
MPN: Essential Tests

- CBC and Clinical information
- Morphology blood and BM
- Blast enumeration blood and BM (lineage determination if increased blasts noted)
- Karyotype
- Molecular: \textit{BCR-ABL1}, \textit{JAK2} and Exon 12, \textit{CALR}, \textit{MPL} (can order on selected basis or sequentially) \textit{CSF3R} for CNL-picture; \textit{FIP1L1-PDGFR\alpha}, etc. for CEL-like picture
MPN: Additional Genetic Testing

• May provide information for prognosis, disease course prediction (e.g., \( ASXL1^m \) accelerates fibrosis in \( JAK2^m \) MPN’s)

• May identify targetable mutation
MPN: Report Features

• Dx with percent blast blood/BM
• Specify stable phase vs transformation
• Molecular genetic features to support diagnosis
• Additional tests needed for “inconclusive/suspected” cases