



WHO Update to Myeloproliferative Neoplasms

Archana M Agarwal, MD,
Associate Professor of Pathology
University of Utah Department of
Pathology/ARUP Laboratories

Myeloproliferative Neoplasms

- The categories of myeloproliferative neoplasms (MPNs) have not significantly changed since 2008
 - Chronic myeloid leukemia (CML), BCR-ABL1+
 - Chronic neutrophilic leukemia (CNL)
 - Polycythemia vera (PV)
 - Primary myelofibrosis (PMF)
 - PMF, prefibrotic/early stage
 - PMF, overt fibrotic stage
 - Essential thrombocythemia (ET)
 - Chronic eosinophilic leukemia, not otherwise specified (NOS)
 - MPN, unclassifiable

*Mastocytosis has been removed

Chronic Myeloid Leukemia (CML), BCR- ABL1+

- Can be diagnosed from peripheral blood along with (9;22)(q34.1;q11.2)
- Bone marrow is essential for karyotype and to confirm the phase of the disease
- Regular monitoring for BCR-ABL1 and genetic progression and resistance to TKI therapy

CML Continued!

- Accelerated phase criteria's are not universally accepted (includes hematologic, morphologic and cytogenetic parameters and genetic evolution)
- Response of Tyrosine kinase inhibitors (TKIs) are included as provisional criteria's
 - Hematologic resistance to first TKI
 - Hematologic, cytogenetic or molecular indications of resistance to two sequential TKIs
- Blast phase still requires at least 20% blast
- However, presence of any lymphoid blasts either in peripheral blood (PB) or bone marrow should raise concern

New Novel Molecular Findings in MPNs

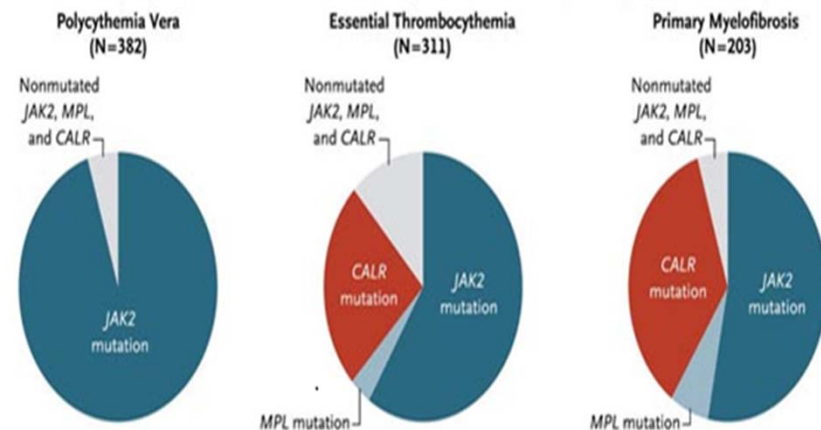
- Calreticulin mutation
- CSF3R mutation

Calreticulin

- Described in 2013, CALR somatic mutations are seen in a large subset of patients with ET or PMF who lack JAK2 and MPL mutations
- **NOT FOUND IN PATIENTS WITH PV**
- Can provide both diagnostic and prognostic information
- The presence of mutations in CALR appears to be associated with **better** outcome in patients with ET
- 80–90% of patients with ET or PMF carry one of the three ‘MPN-driver’ mutations: *JAK2*, *CALR* or *MPL*

Figure A

Distribution of *JAK2*, *MPL*, and *CALR* Mutations in Philadelphia Chromosome–Negative Myeloproliferative Neoplasms



Calreticulin Mutation

- Somatic mutations in CALR, after those in JAK2, are the second most prevailing genetic variation in ET and PMF
- Mutually exclusive from JAK2
- Usually seen in exon 9
- In PMF patients, CALR exon 9 mutations are associated with younger age, **higher platelet count and hemoglobin level, and lower leukocyte count**

CSF3R Mutation

- CSF3R encodes the receptor for colony-stimulating factor 3
- Somatic CSF3R mutations were recently described in **50% to 80% of chronic neutrophilic leukemia (CNL) patients**
- In CNL, the most common mutation is p.T618I, although cytoplasmic truncation mutation can also occur

Chronic Neutrophilic Leukemia(CNL)

- When do we suspect it?
 - Leukocytosis with predominantly neutrophilia
 - No dysgranulopoiesis
 - No increase in blasts or other lineage cells
 - **Presence of CSF3R mutation**

Other Evidence of Clonality

- ASXL1-3% of ET and 13 percent PMF
- TET2- 5% of ET and 17 percent PMF
- DNMT3A-7% of ET and six percent PMF
- SRSF2-3% of ET and 17% PMF

Polycythemia Vera

2008 WHO Criteria

- **Major Criteria:**
- 1. Hb>18.5g/dL for men or 16.5g/dl for woman or other evidence of red cell mass
- 2. Presence of JAK2V617F or JAK2 exon 12 mutation
- **Minor:**
- Bone marrow biopsy showing hypercellularity for age with trilineage proliferation
- Serum Epo below reference range for normal
- Endogenous erythroid colony formation in vitro

Revised WHO Criteria

- **Major criteria:**
- 1. Hb > 16.5 g/dL in men and > 16.0 g/dL in women or, Hematocrit >49% in men >48% in women or, increased red cell mass (RCM)*
- 2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- 3. Presence of JAK2V617F or JAK2 exon 12 mutation
- **Minor criterion:**
- Subnormal serum erythropoietin level

*either all three major or the first two major and the minor

Polycythemia Vera

- Possibly underdiagnosed using only the hemoglobin values
- New proposal is to add hematocrit as one of the criteria
- JAK2 mutations are seen in approximately 99% of cases
- The former minor criteria of endogenous erythroid colony has been removed

Essential Thrombocythemia (ET)

- **Major criteria:**

- Platelet count $> 450 \times 10^9/L$
- Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei no significant increase or left-shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
- Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
- Presence of JAK2, CALR or MPL mutation

- **Minor criterion:**

- Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis of ET requires meeting all four major criteria or the first three major criteria and the minor criterion

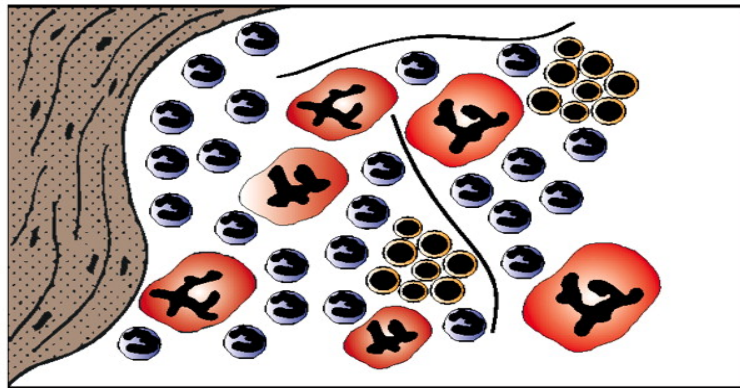
Pre Primary Myelofibrosis

- Has a major overlap with true ET and can be difficult to distinguish as the only clinical finding could be marked thrombocytosis mimicking ET
- However, here reticulin fibrosis is usually >grade 1
- Minor Criteria like anemia, leukocytosis, splenomegaly or increased LDH can be helpful as one minor criteria is required for diagnosis


Distinguishing ET and pre-PMF

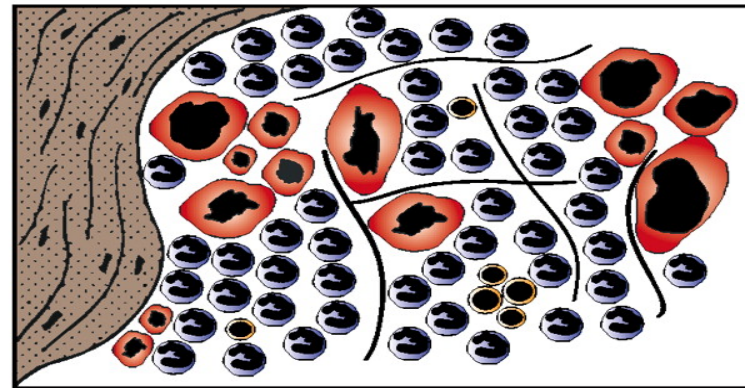
ET





- no or only slight increase in age-matched cellularity
- no significant increase in granulo- and erythropoiesis
- prominent large to giant mature megakaryocytes with hyperlobulated or deeply folded nuclei, dispersed or loosely clustered in the marrow space
- no or very rarely minor increase in reticulin fibers



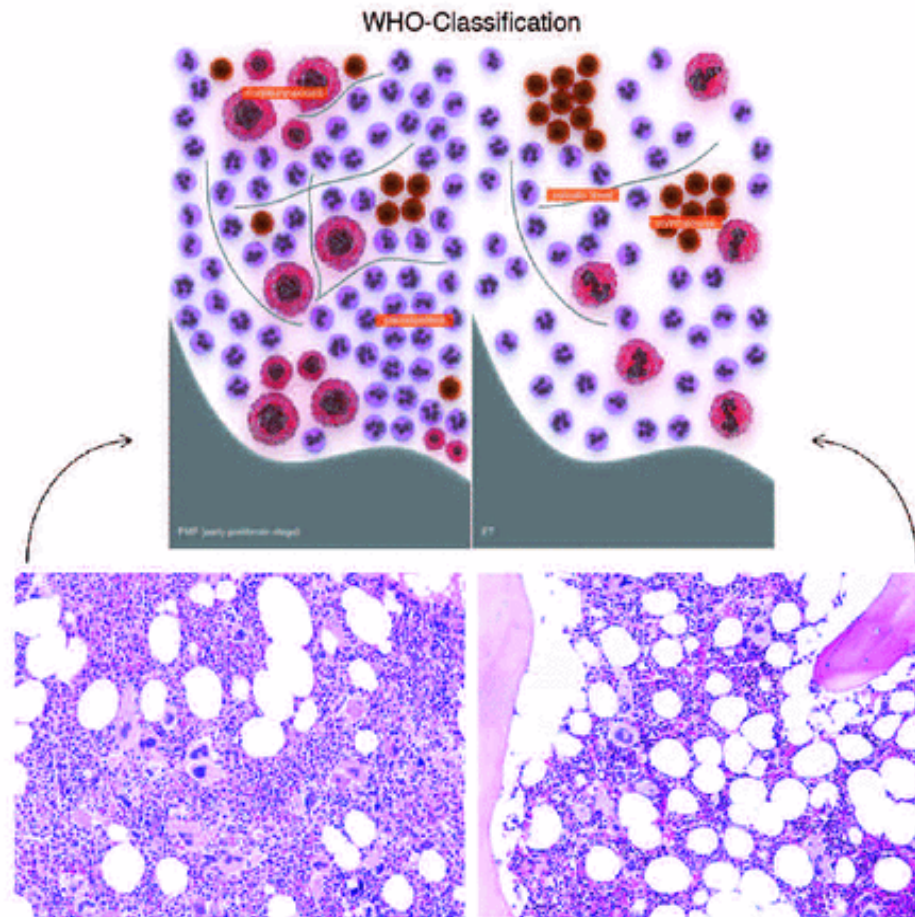
PMF (early-prefibrotic stage)

- marked increase in age-matched cellularity
- pronounced proliferation of granulopoiesis and reduction of erythroid precursors
- dense or loose clustering and frequent endosteal translocation of medium sized to giant megakaryocytes showing hyperchromatic, hypolobulated, bulbous, or irregularly folded nuclei and an aberrant nuclear/cytoplasmic ratio
- 



 Megakaryopoiesis;  Granulopoiesis;  Erythropoiesis;  Reticulin fibers

ET vs prePMF



Advances In Myelofibrosis: A Clinical Case Approach. Mascarenhas JO, Orazi A et al. Haematologica October 2013 98: 1499-1509

Primary Myelofibrosis

- Major criteria:
 - Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
 - Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms
 - Presence of JAK2, CALR or MPL mutation or in the absence of these mutations, presence of another clonal marker ** or absence of reactive myelofibrosis ***
- Minor criteria:
 - Presence of at least one of the following, confirmed in two consecutive determinations:
 - a. Anemia not attributed to a comorbid condition
 - b. Leukocytosis $>11 \times 10^9/L$
 - c. Palpable splenomegaly
 - d. LDH increased to above upper normal limit of institutional reference range
 - e. Leukoerythroblastosis
- Diagnosis of overt PMF requires meeting all three major criteria, and at least one minor criterion

Summary

- Inclusion of CALR plays a very important role in diagnosing ET and PMF
- CSF3R mutation is strongly associated with chronic neutrophilic leukemia
- It is important to distinguish true ET from prePMF as the prognosis is much more favorable in ET

References

- The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Daniel A. Arber, Attilio Orazi, Robert Hasserjian, Jürgen Thiele, Michael J. Borowitz, Michelle M. Le Beau, Clara D. Bloomfield, Mario Cazzola and James W. Vardiman. *Blood* 2016 :blood-2016-03-643544
- Essential thrombocythemia versus early primary myelofibrosis: a multicenter study to validate the WHO classification. Jürgen Thiele, Hans Michael Kvasnicka, Leonhard Müllauer, Veronika Buxhofer-Ausch, Bettina Gisslinger and Heinz Gisslinger. *Blood* 2011 117:5710-5718
- Rationale for revision and proposed changes of the WHO diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis. Barbui T, Thiele J, Vannucchi AM, Tefferi A. *Blood Cancer J.* 2015;5:e337.

Questions!