2016 Updates to the Classification of Myeloid Neoplasms and acute leukemia

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Myeloproliferative neoplasms

- Mutations
- CALR – aberrant and preferential expansion of megakaryocyte lineage, 20–30% of PMF and ET
- Triple negative cases: ASXL1, IDH1/2, EZH2, SRSF2 etc
“Provisional” response–to–TKI criteria
Hematologic resistance to the first TKI or
Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs or
Occurrence of 2 or more mutations in BCR–ABL1 during TKI therapy
Detection of any bonafide lymphoblasts in blood or bone marrow
WHO PV criteria

Major criteria
1. Hemoglobin >16.5 g/dL in men, Hemoglobin >16.0 g/dL in women or, Hematocrit >49% in men Hematocrit >48% in women or, increased red cell mass (RCM)*
2. BM 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

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion
WHO ET criteria

**Major criteria**

1. Platelet count $\geq 450 \times 10^9/L$

2. BM 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

3. Not meeting WHO criteria for BCR-ABL1$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms

4. 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 4 major criteria or the first 3 major criteria and the minor criterion
**WHO prePMF criteria**

**Major criteria**

1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1**, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis

2. Not meeting the WHO criteria for BCR–ABL1⁺ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms

3. Presence of JAK2, **CALR**, or MPL mutation or in the absence of these mutations, presence of another clonal marker,† or absence of minor reactive BM reticulin fibrosis‡

**Minor criteria**

Presence of at least 1 of the following, confirmed in 2 consecutive determinations:

- a. **Anemia not attributed to a comorbid condition**
- b. **Leukocytosis ≥ 11 × 10⁹/L**
- c. **Palpable splenomegaly**
- d. **LDH increased to above upper normal limit of institutional reference range**
WHO overt PMF criteria

**Major criteria**

1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis **grades 2 or 3**

2. Not meeting WHO criteria for ET, PV, BCR–ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms

3. 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 1 of the following, confirmed in 2 consecutive determinations:

a. Anemia not attributed to a comorbid condition

b. Leukocytosis ≥11 × 10⁹/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 3 major criteria, and at least 1 minor criterion.
Chronic neutrophilic leukemia (CNL)

- Presence of CSF3R T618I or other activating CSF3R mutation
Mastocytosis

- Separate disease category
- SM– AHNMD changed to SM– AHN
MDS

- MDS with single lineage dysplasia (MDS–SLD)
- MDS with multilineage dysplasia (MDS–MLD)

**MDS with ring sideroblasts (MDS–RS)** – MDS with SF3B1 mutation can be classified as MDS RS if 5% ring sideroblasts are present

- **MDS with isolated del(5q)** – allows single additional cytogenetic abnormality, TP 53 mutation study or p 53 immunostain.

- MDS with excess blasts (MDS–EB)

**MDS U** – with 1% blood blasts, based on defining cytogenetic abnormality

RCC
The presence of +8, -Y, or del (20q) is not considered MDS defining.

Presence of MDS-associated somatic mutations alone in patients with unexplained cytopenia is not considered diagnostic of MDS

CHIP

Separating MDS from reactive causes of cytopenia and dysplasia.
# Myeloid/lymphoid neoplasms associated with eosinophilia and rearrangements of PDGFRA, PDGFRB, FGFR1 or with PCM1–JAK2

<table>
<thead>
<tr>
<th>Disease</th>
<th>Presentation</th>
<th>Genetics</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>PDGFRA</td>
<td>Eosinophilia</td>
<td>Cryptic deletion at 4q12</td>
<td>Respond to TKI</td>
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<td></td>
<td>↑Serum tryptase</td>
<td>FIP1L1–PDGFRA, at least 66 other partners</td>
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<td>↑Marrow mast cells</td>
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<tr>
<td>PDGFRB</td>
<td>Eosinophilia</td>
<td>t(5;12)(q32;p13.2) ETV6–PDGFRB, at least 25 other partners</td>
<td>Respond to TKI</td>
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<td>Monocytosis mimicking CMML</td>
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<tr>
<td>FGFR1</td>
<td>Eosinophilia</td>
<td>Translocations of 8p11.2</td>
<td>Poor prognosis; do not respond to TKI</td>
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<td>Often presents with T–ALL or AML</td>
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<tr>
<td>PCMI–JAK2</td>
<td>Eosinophilia</td>
<td>t(8;9)(p22;p24.1) PCMI–JAK2</td>
<td>May respond to JAK2 inhibitors</td>
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<td>Rarely presents with T–LBL or B–ALL</td>
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<td>Bone marrow shows left-shifted erythroid</td>
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<td>predominance and lymphoid aggregates</td>
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Myelodysplastic/myeloproliferative neoplasms
CMML

- MDS Vs MPN like
- Refined blast count for prognosis
  - CMML-0, CMML-1, CMML-2
- Mutation of SRSF2, TET2, ASXL1
No changes in criteria

CSF3R mutation (if positive consider CNL)

SETBP1/ETNK1 mutation
I. Clinical and hematologic features (all 4 features mandatory)
   • PB monocyte count $\geq 1 \times 10^9$/L
   • Blast percentage in PB and BM <20%
   • Splenomegaly
   • Absence of Philadelphia chromosome (BCR/ABL1 rearrangement)

II. Genetic studies (1 finding sufficient)
   • Somatic mutation in PTPN11$^*$ or KRAS$^*$ or NRAS$^*$
   • Clinical diagnosis of NF1 or NF1 mutation
   • Germ line CBL mutation and loss of heterozygosity of CBL$^+$

III. For patients without genetic features, besides the clinical and hematologic features listed under I, the following criteria must be fulfilled:
   • Monosomy 7 or any other chromosomal abnormality or at least 2 of the following criteria:
     • Hemoglobin F increased for age
     • Myeloid or erythroid precursors on PB smear
     • GM-CSF hypersensitivity in colony assay
     • Hyperphosphorylation of STAT5
MDS/MPN–RS–T

- Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, ≥15% ring sideroblasts,* <1% blasts in PB and <5% blasts in the BM
- Persistent thrombocytosis with platelet count ≥450 × 10⁹/L
- Presence of a SF3B1 mutation or, in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features‡
  - No BCR–ABL1 fusion gene, no rearrangement of PDGFRA, PDGFRB, or FGFR1; or PCM1–JAK2; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡
  - No preceding history of MPN, MDS (except MDS–RS), or other type of MDS/MPN
AML

- AML, not otherwise specified
- Acute erythroid leukemia, erythroid/myeloid type has been removed
- Myeloblasts are counted as percentage of total marrow cells
- Majority of such cases have <20% total blast cells and are now classified as MDS
- Close biologic relationship of erythroid/myeloid type to MDS
Two new provisional entities
AML with BCR-ABL1
AML with mutated RUNX1

Prolonged to full entities
AML with NPM1 mutation
AML with CEBPA mutation
AML

AML with BCR–ABL1
- 0.5%–3% of AML
- recognize the denovo cases who benefit from TKI therapy
  - AML, NOS > AML MRC > CBFL
- differentiating from CML
- prognosis
AML with mutated RUNX1

- not associated with MDS related cytogenetic abnormalities
- worse prognosis than other AML types
- high number of AML with minimal differentiation
- dysplasia +/-
- AML with NPM1 mutation—If NPM1 mutation identified, diagnose as AML with NPM1 mutation
- AML with CEBPA mutation—if biallelic CEBPA mutation, diagnose as AML with CEBPA mutation
- If AML MRC is diagnosed based on history of MDS or MDS related cytogenetics, then retain AML–MRC even if NPM1, biallelic CEBPA mutations are identified.
AML with myelodysplasia-related changes

- Multilineage dysplasia alone will not qualify as AML MRC, when a NPM1 mutation/CEBPA mutation is present.
- In cases lacking these mutations, morphological detection of multilineage dysplasia is sufficient.
- del(9q) has been removed as a defining cytogenetic abnormality for AML with myelodysplasia-related changes.
≥50% or more erythroid cells, ≥20% total myeloblasts usually meet criteria for AML–MRC

If not meeting criteria for AML–MRC or AML with recurrent genetic abnormalities–subtype of AML, NOS.

Pure erythroid leukemia is now the only type of acute erythroid leukemia.
Myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction

- AML with germ line CEBPA mutation
- Myeloid neoplasms with germ line DDX41 mutation

Myeloid neoplasms with germline predisposition and preexisting platelet disorders

- Myeloid neoplasms with germ line RUNX1 mutation
- Myeloid neoplasms with germ line ANKRD26 mutation
- Myeloid neoplasms with germ line ETV6 mutation

Myeloid neoplasms with germline predisposition and other organ dysfunction

- Myeloid neoplasms with germ line GATA2 mutation
- Myeloid neoplasms associated with BM failure syndromes
- Myeloid neoplasms associated with telomere biology disorders
- JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome–like disorders
- Myeloid neoplasms associated with Down syndrome
Acute leukemias of ambiguous lineage

- The small list of specific lineage markers useful for defining MPAL is unchanged
- In cases with 2 distinct blast population, it is not necessary that the specific markers be present
- B ALL with low level MPO
**B- ALL**

- **B ALL with intrachromosomal amplification of chromosome 21**
- **BCR– ABL1 like B– ALL**
B ALL with intrachromosomal amplification of chromosome 21– FISH with a probe for the RUNX1 gene, older children with low WBC counts, adverse prognosis, overcome with more aggressive therapy.
BCR–ABL1 like B–ALL– adverse prognosis, responses of some cases to TKI therapies, exhibits gene expression profile similar to BCR–ABL1 positive ALL, more likely in males, Down syndrome and higher MRD levels post induction.

B–ALL with low hypodiploidy is characterised by high frequency of TP53 mutations
**T- ALL**

- Early T precursor ALL
- By definition, blasts in ETP ALL express CD7 but lack CD1a and CD8, positive for 1 or more myeloid/stem cell markers CD34, CD117, HLADR, CD13, CD33, CD11b, or CD65.
- CD5 is often negative and when positive is present on <75% of the blast population.
- largest series to date, no prognostic significance.
Natural killer (NK) cell lymphoblastic leukemia/lymphoma
Mimic T-lymphoblastic lymphoma.

Lymphoid tissue of the upper aerodigestive tract.

Phenotype reflects a developmentally normal, nonaberrant phenotype and the proliferations are not clonal.

Associated with castleman disease, follicular dendritic cell sarcoma, AITL
iT-LBP

- Confluent groups of TdT positive T lymphoblasts
- Relative preservation of normal architecture
- Absence of morphologic atypia
- Absence of thymic epithelium
- Nonclonal population
- Developmentally normal thymic T cells
- Indolent clinical course
References


Thank you