WHO Klassifikation der MDS/MPN
- Histologie -

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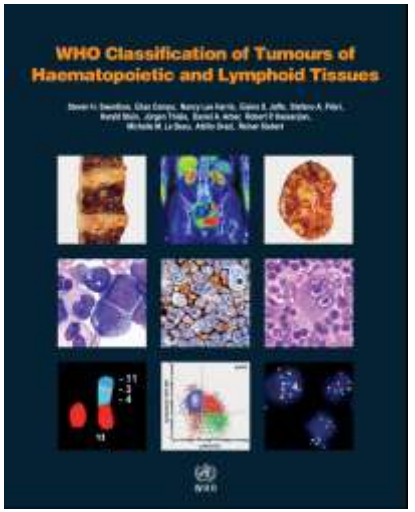
Principles and rationale of the WHO 2016 classification (updating the 4th edition)



- the WHO classification emphasizes the identification of distinct clinicopathological entities, rather than just being a "cell of origin" classification
- stresses an "**integrated approach**" to disease definition by incorporation of **key available information** including morphology, molecular and cytogenetic findings, immunophenotype, and clinical features
- the work of a large number of hemato-pathologists, but developed with the active advice and consent of clinicians

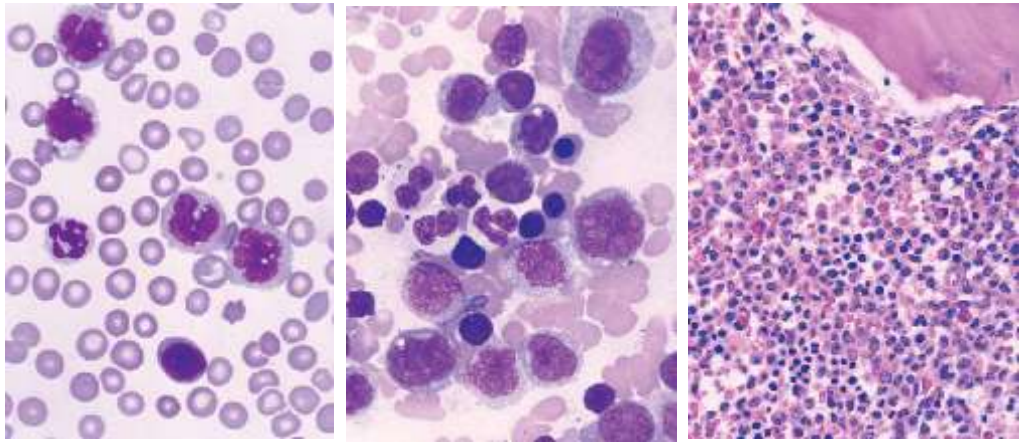
Chronic myelomonocytic leukemia (CMML)

- **bone marrow features**

  hypercellular with monocytic and granulocytic proliferation

  myeloblasts/monoblasts

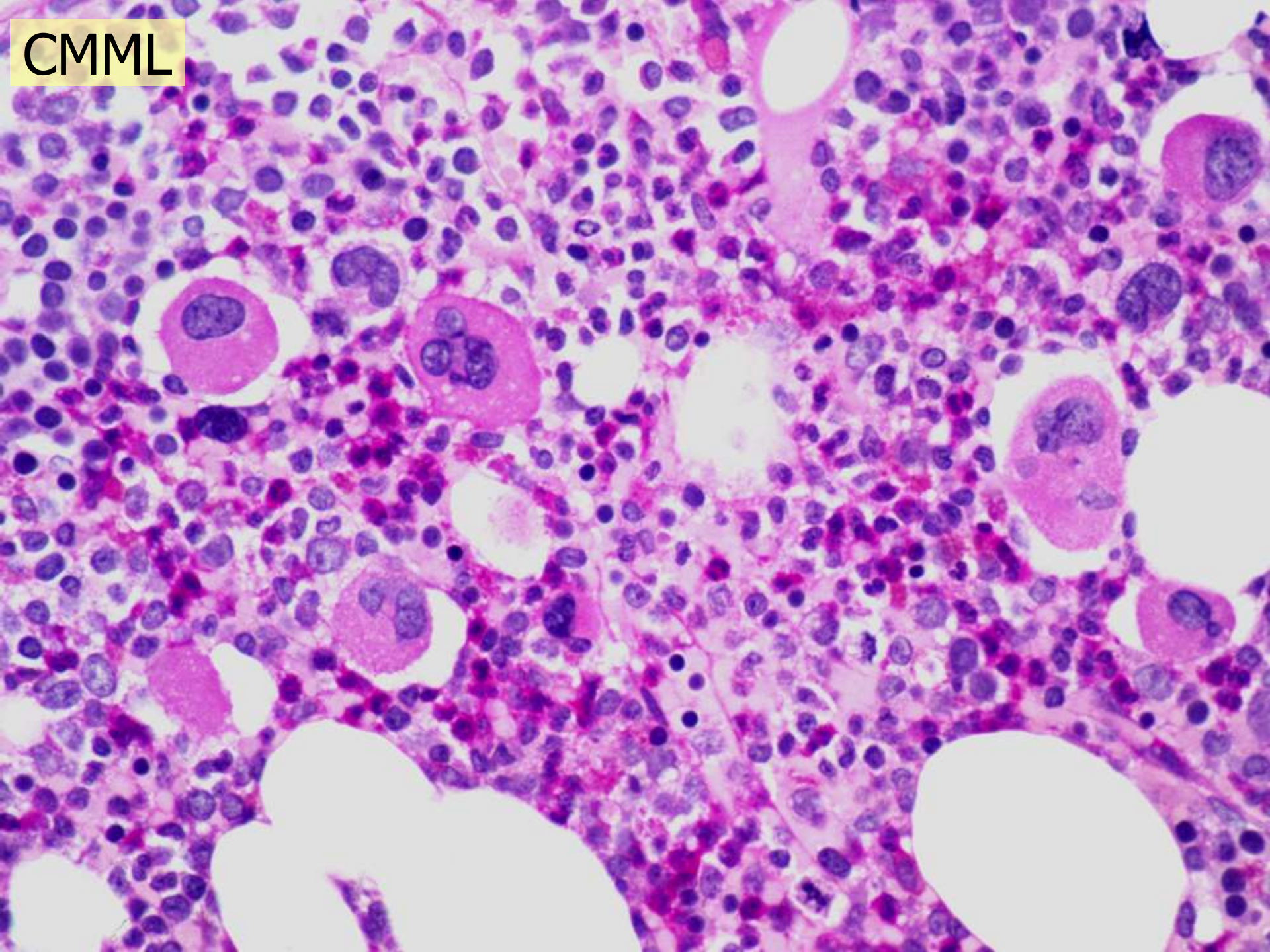
  - CMML-0 < 5%
  - CMML-1 < 10%
  - CMML-2 < 20%

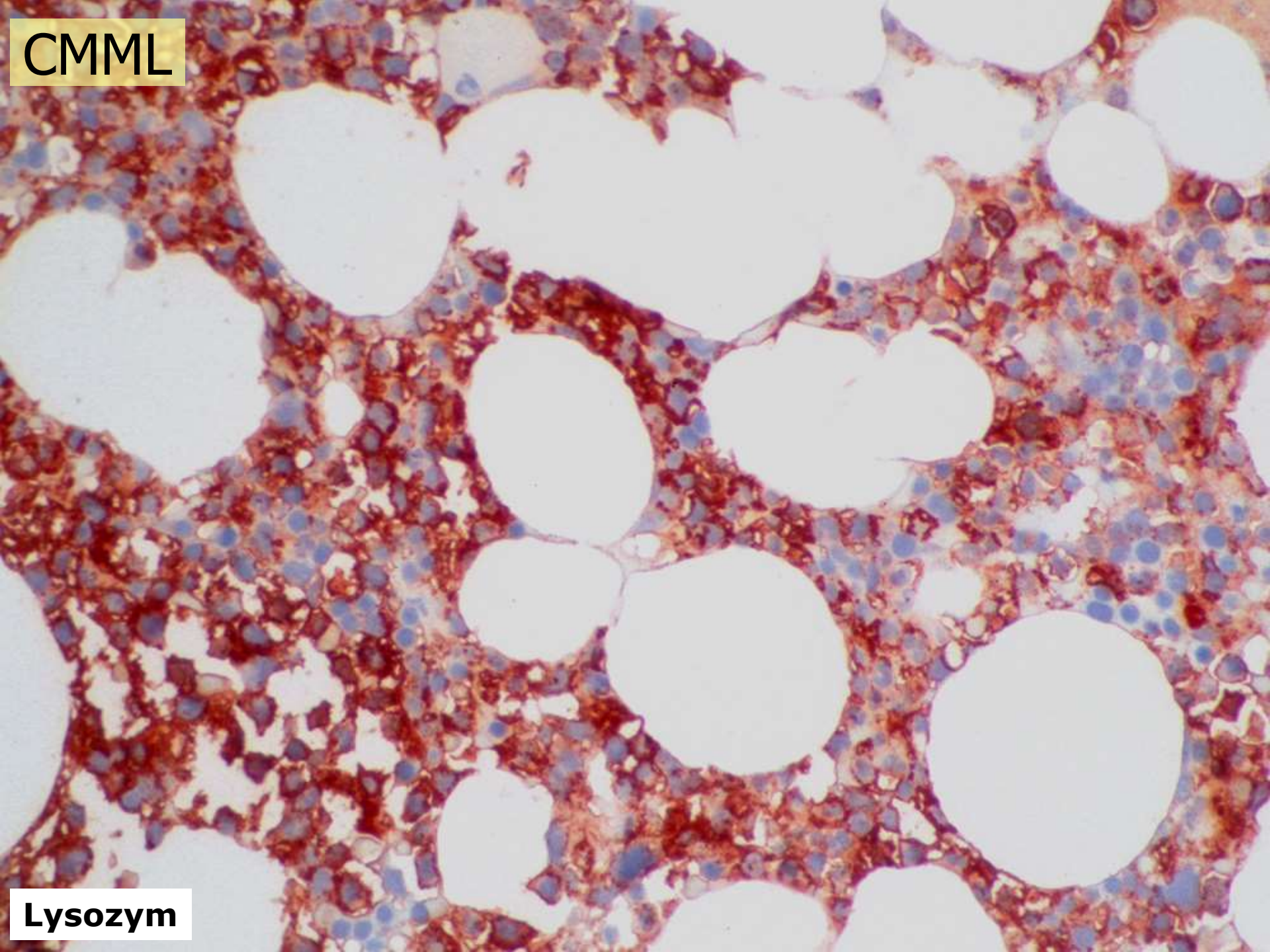


  erythroid precursors >15%

  increase in reticulin fibers in 30%

  erythroid and megakaryocytic dysplasia


CMML


CMML
Lysozym

WHO 2016 Updates to CMML

- Additional PB requirement of ≥10% monocytes
- Integration of mutations could help supporting a CMML diagnosis (particularly TET2 plus SRSF2) and/or prognostic information (ASXL1)

- **MDS- vs. MPN-like**
  - **CMML dysplastic** (WBC, <13 $\times 10^9$/L)
  - **CMML proliferative** (≥13 × 10^9/L); this subtype has more frequent RAS or JAK2 mutations and splenomegaly

- **Refined blast count**
  - CMML-0: <2% blasts in PB; <5% blasts in BM
  - CMML-1: 2–4% blasts in PB; 5–9% blasts in BM
  - CMML-2: 5–19% blasts in PB; 10–19% in BM, or when Auer rods are present irrespective of the blast count

Ricci C et al. Clin Cancer Res. 2010 ; Schuler E, et al. Leuk Res. 2014; Cervera N, et al. Am J Hematol. 2014 Jun;89(6):604-9.
Meggendorfer M et al. Blood 2012; Itzykson R et al. J Clin Oncol 2013; Federmann B et al. Hum Pathol. 2014;
Patel B et al. Int J Hematol. 2015; Gerstung M, et al. Nat Commun. 2015

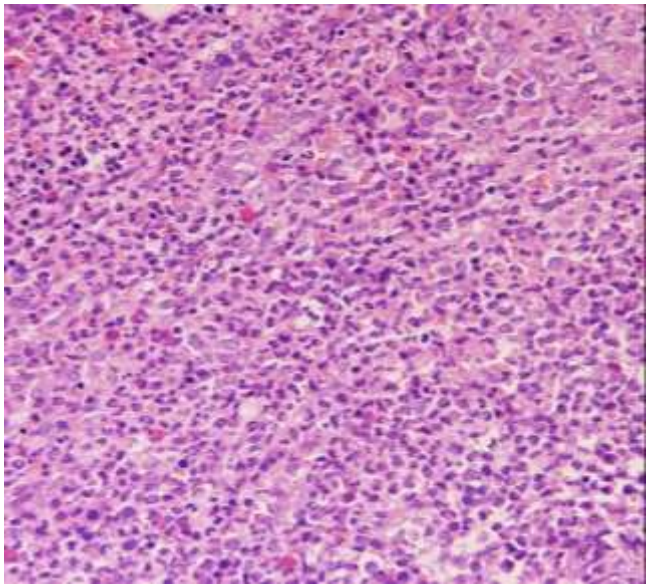
aCML becomes a better defined entity

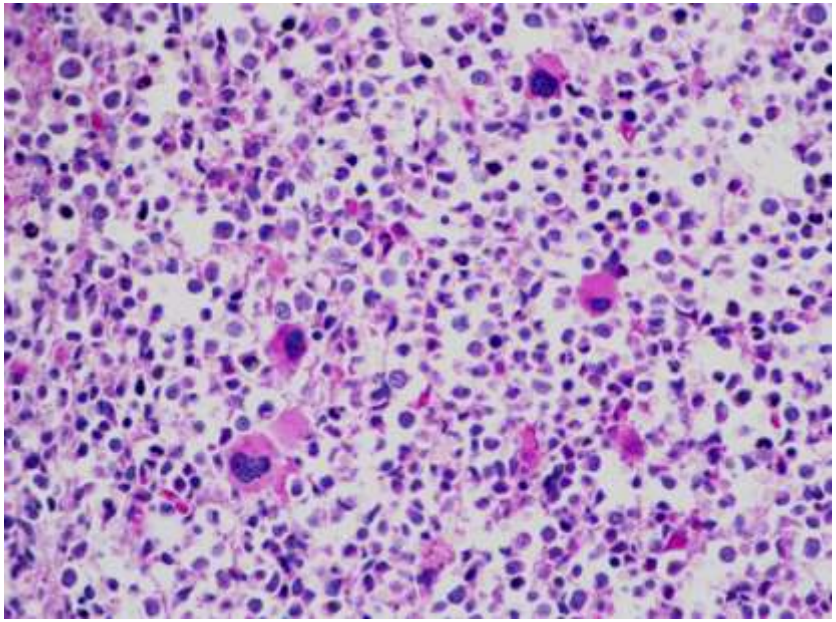
- It has its own molecular profile:
  - ***SETBP1*** mutations in 15-32% and *ETNK1* mutations in 9% *ETNK1* coexistent with *SETBP1* in 33%
  - *JAK2, CALR* mutations rare or absent
  - ***CSF3R* mutations absent or very rare** (<10%)
- Can be separated from other MDS/MPN subtypes and from MPN (e.g., CNL, cases of MPN in AP)
- aCML has poorer survival than other MDS/MPN or MPN; novel targeted approaches much needed
- Main distinction is with chronic neutrophilic leukemia (CNL)

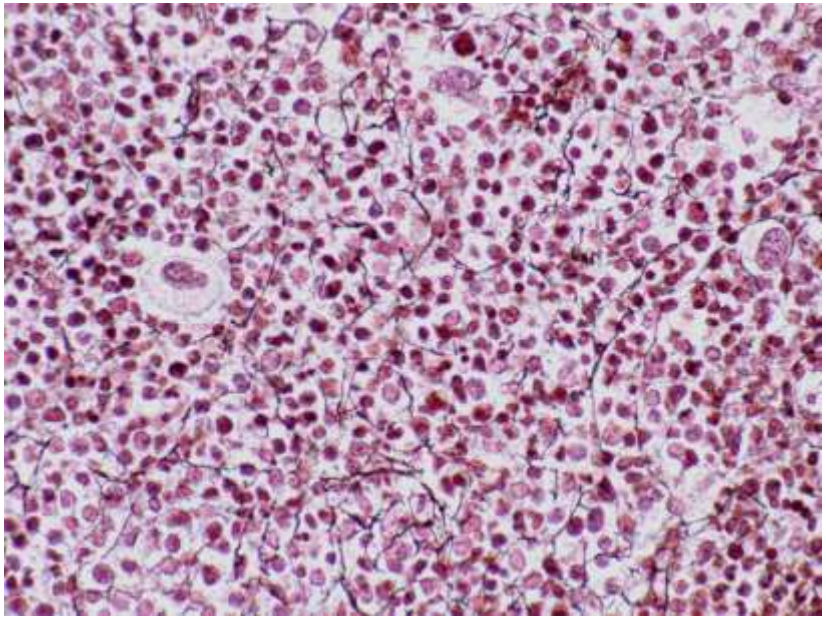
Wang SA et al. Blood 2014;123:2645; Piazza R et al. Nat Genet 2013;45:18; Gotlib J et al. Blood 2013;122:1707;
Maxson JE et al. NEJM 2013;368:1781, Pardanani A et al. Leukemia 2013;27:1870; Gambacorti-Passerini CB, et al. Blood. 2015; 125:499.

BM histology in aCML

- **hypercellular with predominance of the granulocytic series**
  - increase in myeloid precursors
  - reduced erythropoiesis
  - variable degree of reticulin fibrosis
- **dysplastic megakaryocytes**







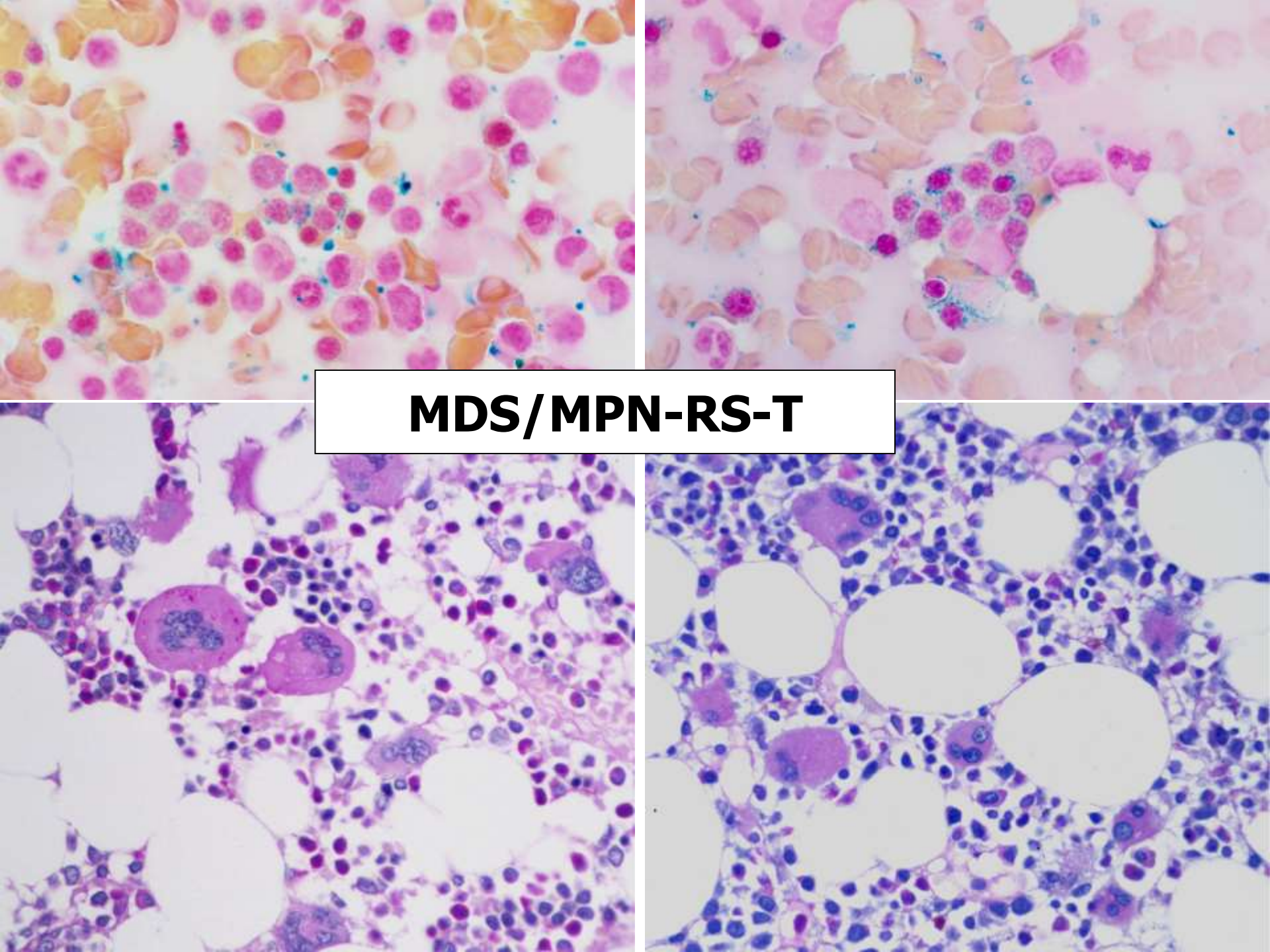
Diagnostic criteria for aCML (Update 2016)

- Peripheral blood leukocytosis due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes, metamyelocytes ≥10% of leukocytes)
- Dysgranulopoiesis, which may include abnormal chromatin clumping
- Not meeting WHO criteria for *BCR-ABL1*-positive chronic myelogenous leukaemia, primary myelofibrosis, polycythemia vera or essential thrombocythemia[a]
- No rearrangement of *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2*
- No or minimal absolute basophilia; basophils usually <2% of leukocytes
- No or minimal absolute monocytosis; monocytes <10% of leukocytes
- Hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages.
- Less than 20% blasts in the blood and bone marrow

Cases of PV or ET particularly if in accelerated phase and/or in Post-PV or Post-ET myelofibrotic stage, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the bone marrow and/or MPN-associated mutations (in *JAK2, CALR* or *MPL*) tends to exclude a diagnosis of aCML.

A diagnosis of aCML is supported by the presence of *SETBP1 and/*or *ETNK1* mutations. The presence of *CSF3R* mutations is uncommon in aCML; if detected, it should prompt a careful morphologic review to exclude an alternative diagnosis of CNL or other myeloid neoplasm.

Arber et al., Blood (2016) 127:2391-2405


MDS/MPN-RS-T

MDS/MPN-RS-T: now promoted to a full entity

MPN-like

- Clinical presentation
  - Thrombocytosis
  - Need for cytoreduction
- BM morphology
  - Large megakaryocytes with bulbous nuclei
- Genetic profile
  - JAK2 mutation (50-60%)
  - Rare CALR/MPL

MDS-like

- Clinical presentation
  - Macrocytic anemia
  - Transfusion requirement
- BM morphology
  - Erythroid dysplasia
  - Ring sideroblasts
- Genetic profile
  - SF3B1 mutation (80-90%)

Schmitt-Graeff A Haematologica 2008; Wang SA Leukemia 2006; Malcovati L Blood 2011 and Blood. 2014 Jeromin S Haematologica 2015; Zoi K Int J Hematol. 2015.

Diagnostic criteria for MDS/MPN-RS-T (Update 2016)

- Anaemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, **≥15% ring sideroblasts***, <1% blasts in peripheral blood and <5% blasts in the bone marrow
- Persistent thrombocytosis with platelet count ≥450 x 10^9/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

***≥15% ring sideroblasts required even if *SF3B1* mutation is detected**

**A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of *SF3B1* mutation together with a mutation in *JAK2* V617F, *CALR* or *MPL* genes

***In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del(5q)- No or minimal absolute basophilia; basophils usually <2% of leukocytes

Arber et al., Blood (2016) 127:2391-2405

Summary: Revision of MDS/MPN

- Refractory anemia with ring sideroblasts associated with marked thrombocytosis (MDS/MPN-RS-T)
  - Moved from a provisional to a full entity and new name
  - Common co-mutation of JAK2 and SF3B1
- Atypical CML, *BCR-ABL1* negative (aCML)
  - Integration of NGS: SETBP1, CSF3R, ETNK1
  - CNL: common co-mutation CSF3R/SETBP1
- Chronic myelomonocytic leukemia (CMML)
  - Mutation profile (SRSF2/TET2/ASXL1) helpful in supporting diagnosis and providing prognosis
  - Cases with NPM1 mutation or 11q23 rearrangement should be followed carefully for AML
  - Emphasize careful blast/ promonocyte/monocyte count to distinguish from AML
  - CMML-0,-1,-2; CMML MDS and MP subtypes

Mutations are insufficient to diagnose MDS/MPN on their own

They rather represent a usefully complement to a clinicopathologic-based diagnosis

Arber et al., Blood (2016) 127:2391-2405