What’s New in Hematopathology

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What’s New in Hematopathology part 2 focuses on changes to myeloid neoplasms important for your practice, plus emerging areas of interest. It includes highlights from the revised WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition, 2017, European Leukemia Network and American Society for Hematology (ASH) and College of American Pathologists (CAP) guidelines for diagnosis of acute leukemias.

Myeloid Neoplasms with Germline Predisposition

- This is a new WHO section; mutation alone without morphologic findings of myeloid neoplasia is not sufficient.
- 3 categories are distinguished:
  - Without pre-existing disorder/organ dysfunction (e.g. DDX41*, AML with germline CEBPA).
  - With pre-existing platelet disorder (e.g. ANKRD26*, ETV6*, RUNX1* (Fig. 1)).
  - With other organ dysfunction (e.g. GATA2, bone marrow failure syndromes, Down syndrome*).

  *Lymphoid neoplasms also reported.

Acute Myeloid Leukemia (AML)

- Guidelines from CAP and ASH on initial acute leukemia workup (Arch Pathol Lab Med 2017;141:1342): Conventional cytogenetics remain the standard of care.
- Molecular testing:
  - Actionable targets: FLT3-ITD and TKD (recommended for all AML), IDH1/2.
  - Consider testing TET2, WT1, DNMT3A, TP53 (European Leukemia Network guidelines): test for KIT mutations in core binding factor AML (worse prognosis).
  - Diagnostic of AML even with < 20% blasts if t(8;21), inv(16), t(16;16) or PML-RARA present.

- 8 categories of AML, 3 defined by molecular characteristics.
  - AML with biallelic mutated CEBPA: Better prognosis; single mutations do not count.
  - AML with mutated NPM1: High NPM1 mutant allele burden at diagnosis may correlate with minimal residual disease at first remission and a worse prognosis (Blood 2018;131:2816, Am J Hematol 2019;94:921).
  - AML with mutated RUNX1 (provisional): Worse prognosis; MDS related cytogenetics or prior therapy takes precedence for diagnosis.
  - AML with myelodysplasia related changes: Prior MDS, specific cytogenetic abnormalities (del(9q) and monosomy 5 removed) or multilineage dysplasia.
  - Therapy related AML: Should designate along with any specific genetic abnormality.
  - AML with BCR-ABL1 (provisional): A type of de novo AML (must exclude CML), most are p210 fusions, additional cytogenetic abnormalities common; may benefit from tyrosine kinase inhibitor (TKI) therapy.

- Acute erythroid leukemia, erythroid/myeloid type: Removed as subcategory of AML, NOS; myeloblasts should always be counted as a percentage of total marrow cells.
- Minimal residual disease in AML: Independent prognostic indicator for risk stratification and treatment; can be performed through flow cytometric or molecular techniques (Blood 2018;131:1275).

Myelodysplastic Syndrome (MDS)

- Diagnostic categories no longer refer to the specific type of cytopenia; complete karyotype critical for determining prognosis.
- MDS del(5q): The only cytogenetic or molecular abnormality that defines an MDS subtype, can have 1 other chromosomal abnormality - except monosomy 7 or del(7q); TP53 mutation identifies adverse prognostic subgroup.
- MDS with ring sideroblasts (MDS-RS): If SF3B1 mutation, ≥ 5% ring sideroblasts sufficient for diagnosis.
- NPM1 mutated myeloid neoplasms with < 20% blasts are rare but appear biologically distinct; patients may demonstrate an aggressive course and benefit from more intensive therapeutic regimens (Blood Adv 2019;3:1540, Blood Adv 2019;3:922) (Fig. 2).
Myeloproliferative Neoplasms (MPN)

- Chronic myeloid leukemia (CML), BCR-ABL+: Chronic phase can largely be diagnosed on peripheral blood with detection of BCR-ABL1 but bone marrow essential for complete karyotype and morphologic confirmation of disease phase.
- Accelerated phase: Criteria include additional clonal chromosomal abnormalities at diagnosis in Ph(+) cells and provisional criteria related to TKI response.
- BCR-ABL negative MPNs: CALR mutations provide proof of clonality and have prognostic significance in addition to JAK2 and MPL; JAK2 V617F is not specific for any MPN type and can rarely be seen in de novo AML and MDS.
- Semi-quantitative grading for bone marrow fibrosis now includes collagen and osteosclerosis in addition to reticulin (Histopathology 2016;68:905).
- Chronic neutrophilic leukemia: Rare, strongly associated with CSF3R mutation, often together with SETBP1 or ASXL1; JAK2 V617F reported in a subset.
- Polycythemia vera (PV): Revised hemoglobin criteria to avoid under diagnosis (> 16.5 g/dL men, > 16.0 g/dL women); bone marrow morphology is a reproducible criterion for diagnosis.
- Primary myelofibrosis (PMF): Prefibrotic PMF now includes minor clinical criteria (anemia, leukocytosis, palpable splenomegaly, elevated LDH) to help differentiate from essential thrombocytemia.
- PMF with absolute monocytosis (15% of cases) associated with worse outcome (Br J Haematol 2018;183:835).
- Chronic eosinophilic leukemia, NOS (CEI): Must have clonal abnormality; increased blasts (≥ 5% bone marrow or ≥ 2% peripheral blood); excludes rearrangements of PDGFRα/PDGFRβ, FGFR1, PCM1-JAK2, ETV6-JAK2, BCR-JAK2 (Fig. 3).

Myeloid / Lymphoid Neoplasms with Eosinophilia

- Myeloid / lymphoid neoplasms associated with eosinophilia and rearrangement of PDGFA, PDGFRB or FGFR1 or with PCM1-JAK2: Diagnosis does not require eosinophilia and may be absent in a subset.
- Myeloid neoplasms with t(8;9)(p22;p24.1); PCM1-JAK2 (provisional): Rarely presents as B or T lymphoblastic leukemia; responds to JAK2 inhibitors.
- ETV6-JAK2 and BCR-JAK2 neoplasms more frequently present as B lymphoblastic leukemia and best included in the new category BCR-ABL1-like B-ALL.
- STAT5B: Recurrent activating STAT5B N642H mutations now described in myeloid neoplasia with eosinophilia (Leukemia 2019;33:415) (Fig. 3).

MDS / MPN

- MDS / MPN with ring sideroblasts and thrombocytosis: Formerly RARS-T, now accepted as a full entity, ≥ 15% ring sideroblasts required even if SF3B1 mutation in contrast to MDS-RS.
- Chronic myelomonocytic leukemia (CMML): Blast percentage of prognostic import, now stratify as CMML-0, -1 or -2; molecular and clinical differences between proliferative type (WBC count ≥ 13 × 10⁹/L) and dysplastic type (WBC < 13 × 10⁹/L) (Blood Adv 2018;2:1807); TET2, SRSF2, ASXL1 mutations common; ASXL1 mutations associated with worse prognosis.
- MDS / MPN unclassifiable: Features of an overlap syndrome but do not meet criteria for defined WHO entities; NOT for evolution of dysplasia in a previously defined MPN.
- MDS / MPN unclassifiable with isolated isochromosome 17q: < 20% blasts and not meeting criteria for CMML or other well defined category, may have distinct clinicopathologic features and poor prognosis (Oncotarget 2016;7:14251).
- Atypical CML: SETBP1 or ETNK1 mutations; generally lack SF3R mutations.

Mastocytosis

- New category, separate from MPN.
- Revised nomenclature for combined disorders: systemic mastocytosis with an associated hematological neoplasm (SM-AHN).
- AHN is often an aggressive neoplasm that must be treated and should be separately indicated in a distinct diagnostic line.
- Critical to distinguish indolent from advanced forms of systemic mastocytosis.

Meet the Authors

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