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WHAT'S NEW IN PATHOLOGY?

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THE LATEST NEWS IN HEMEPATH

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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.*

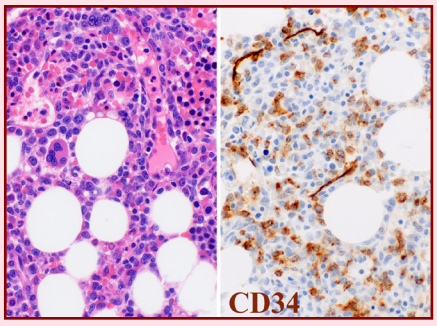

***Fig. 1**: AML with germline* RUNX1 *mutation.*

- Specific underlying genetic defect or predisposition syndrome should be noted as part of the diagnosis.

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**).

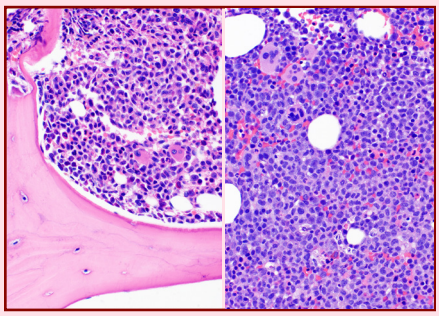

***Fig. 2**: Chronic myelomonocytic leukemia-2 with an* NPM1 *mutation and rapid progression to acute myeloid leukemia.*

Myeloproliferative Neoplasms (MPN)

- **Chronic myeloid leukemia (CML), *BCR-ABL1*$^+$:** 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.
- **Semiquantitative 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 thrombocythemia.
- **PMF with absolute monocytosis** (15% of cases) associated with worse outcome (Br J Haematol 2018;183:835).
- **Chronic eosinophilic leukemia, NOS (CEL):** Must have clonal abnormality; increased blasts (≥ 5% bone marrow or ≥ 2% peripheral blood); excludes rearrangements of *PDGFRA/PDGFRB*, *FGFR1*, *PCM1-JAK2*, *ETV6-JAK2*, *BCR-JAK2* (**Fig. 3**).

Myeloid / Lymphoid Neoplasms with Eosinophilia

- **Myeloid / lymphoid neoplasms associated with eosinophilia and rearrangement of *PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2*:** Diagnosis does not require eosinophilia and may be absent in a subset.
- **Myeloid neoplasm 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 × 10^9/L) and dysplastic type (WBC < 13 × 10^9/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 *CSF3R* mutations.

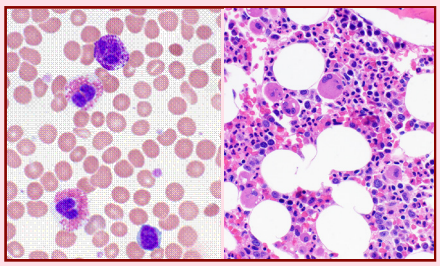

***Fig. 3**: Peripheral blood with eosinophilia and bone marrow with dysplastic megakaryopoiesis in a patient with a* STAT5B N642H *mutation and chronic eosinophilic leukemia, NOS.*

- **Juvenile myelomonocytic leukemia**: Mutually exclusive genetic aberrations that alter RAS/MAPK pathway (*PTPN11*, *KRAS*, *NRAS*, *CBL* or *NF1*).

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

Dr. Crane is an Assistant Professor of Pathology at Weill Cornell and serves as Section Editor for Hematopathology at PathologyOutlines.com and Archives of Pathology and Laboratory Medicine. She is passionate about pathology education and outreach, including through the Society of Hematopathology where she serves on the education committee. She can be found on twitter @evemariecrane.

Dr. Patel joined Weill Cornell after completing clinical and research training as the first Geraldine S. Pinkus translational research fellow in hematopathology at the Brigham and Women's Hospital / Dana-Farber Cancer Institute. For recent work, he has been awarded the David Y. Mason Award from the European Association for Haematopathology and the Benjamin Castleman Award from the United States and Canadian Academy of Pathology. He is passionate about pathology education and mentorship and can be found on twitter @SanjayPatelMD.