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Review Article

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Overlap Syndromes of Myeloid Neoplasms: Pathobiology, Diagnosis, and Therapeutic Implications

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ABSTRACT

Myeloid neoplasms encompass a spectrum of clonal hematopoietic stem cell disorders characterized by dysregulated proliferation and differentiation. Among these, overlap syndromes particularly myelodysplastic/myeloproliferative neoplasms (MDS/MPN) represent a biologically and clinically heterogeneous group that straddles the boundaries between myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). Advances in molecular profiling have refined diagnostic criteria and revealed shared pathogenic mechanisms that unify and distinguish these entities. This review summarizes recent insights into the molecular landscape, diagnostic challenges, and evolving therapeutic approaches to MDS/MPN overlap syndromes.

Introduction

Overlap syndromes of myeloid neoplasms, primarily represented by MDS/MPN, exhibit concurrent features of ineffective hematopoiesis and myeloproliferation. The 5th edition of the WHO classification (2022) and the International Consensus Classification (ICC, 2022) recognize several major subtypes: chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML, BCR: ABL1–), MDS/MPN with SF3B1 mutation and thrombocytosis (MDS/MPN-T), juvenile myelomonocytic leukemia (JMML), and MDS/MPN unclassifiable (MDS/MPN-U) [1,2].

Molecular Pathogenesis

The genomic landscape of MDS/MPN overlap syndromes demonstrates substantial overlap with both MDS and MPN, yet with distinctive mutational constellations.

- Common driver mutations involve genes regulating epigenetic modification (TET2, ASXL1, DNMT3A), splicing (SRSF2, SF3B1, U2AF1), signal transduction (RAS pathway, JAK2, CBL), and transcriptional control (RUNX1, SETBP1).
- CMML is characterized by frequent TET2 and SRSF2 co-mutations, which cooperate to drive monocytosis and clonal dominance [3].
- aCML often harbors SETBP1 and ETNK1 mutations, along with aberrations in CSF3R, linking it to dysregulated granulocytic proliferation [4].
- MDS/MPN-T shares features with essential thrombocythemia and MDS, typically associated with SF3B1 and JAK2V617F mutations [5].

These findings suggest that the clonal hierarchy and sequence of mutations determine whether the clinical phenotype leans toward dysplasia, proliferation, or both.

Diagnostic Approach

Diagnosis relies on an integrated assessment of morphology, cytogenetics, molecular genetics, and clinical features.

- Bone marrow morphology typically shows both hypercellularity and dysplasia.
- Flow cytometry aids in distinguishing CMML from reactive monocytosis.
- Next-generation sequencing (NGS) has become indispensable for identifying driver mutations and refining disease classification [6].

Recent guidelines emphasize the need to exclude BCR: ABL1-positive CML and PDGFRA/B or FGFR1 rearrangements, which define distinct entities responsive to targeted therapy [1].

Clinical Course and Prognosis

Overlap syndromes exhibit variable clinical courses, ranging from indolent to rapidly progressive forms.

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- CMML displays a dual nature — proliferative versus dysplastic subtypes — with prognosis influenced by mutational burden, cytogenetic abnormalities, and blast percentage [7].
- aCML generally follows an aggressive course with a high risk of transformation to acute myeloid leukemia (AML).
- MDS/MPN-T often has a relatively favorable prognosis compared to other overlap syndromes, especially in the presence of SF3B1 mutations.

Prognostic models, such as CPSS-mol for CMML and Mayo aCML score, incorporate molecular and clinical variables to stratify risk [8,9].

Therapeutic Approaches

Treatment strategies remain challenging due to disease heterogeneity.

- Hypomethylating agents (HMAs), such as azacitidine and decitabine, are standard options for higher-risk disease, especially in CMML [10].
- Targeted therapies are emerging:
- RAS pathway inhibitors and JAK inhibitors show promise in subsets with pathway activation [11].
- IDH1/2 inhibitors, venetoclax, and splicing modulators are under investigation in molecularly selected cohorts.
- Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option, though limited to fit patients.

Future Directions

Single-cell transcriptomic and spatial multi-omics approaches are redefining our understanding of MDS/MPN pathogenesis by elucidating clonal architecture, microenvironmental interactions, and lineage plasticity. Integration of these technologies with clinical data will be pivotal in developing personalized therapeutic strategies.

Conclusions

Overlap syndromes of myeloid neoplasms embody the complexity of hematopoietic transformation, lying at the interface of dysplasia and proliferation. Advances in genomics and classification systems have improved diagnostic precision and prognostication, yet therapeutic innovation remains an unmet need. Continued efforts in translational and clinical research are essential to unravel disease heterogeneity and identify actionable molecular vulnerabilities.

References

1. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022. 36: 1703-1719.
2. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood, The Journal of the American Society of Hematology. 2022. 140: 1200-1228.
3. Malcovati L, Cazzola M. The molecular basis of CMML. Blood. 2023. 141: 502-514.
4. Maxson JE, Tyner JW. Genomic landscape of atypical CML. Leukemia. 2024. 38: 217-229.
5. Patnaik MM, Tefferi A. MDS/MPN with SF3B1 mutation and thrombocytosis: a distinct clinicopathologic entity. Blood Cancer J. 2023. 13: 45.
6. Itzykson R, Kosmider O. Diagnostic algorithms and molecular profiling in MDS/MPN overlap syndromes. Haematologica. 2023. 108: 2102-2112.
7. Elena C, Galli A, Such E. Clinical and molecular predictors of survival in CMML. Blood. 2016. 128: 408-416.
8. Such E, Germing U, Malcovati L. Development and validation of the CPSSmol prognostic model for CMML. Leukemia. 2021. 35: 172-181.
9. Patnaik MM, Barraco D, Lasho TL. Mayo prognostic model for atypical CML. Leukemia. 2021. 35: 2235-2243.
10. Garcia-Manero G, Fenaux P, Platzbecker U. Hypomethylating agents in MDS/MPN. Blood Rev. 2022. 56: 100969.
11. Meggendorfer M, Alpermann T, Haferlach C. Molecular pathways and targeted therapies in MDS/MPN overlap. Nat Rev Clin Oncol. 2024. 21: 125-140.