Is Morphology Still the Basis for MDS Diagnosis and Follow-up?

No

Robert P Hasserjian

Myelodysplastic syndromes (MDS) were originally described in the FAB classification as syndromes of unexplained cytopenia accompanied by distinctive morphologic abnormalities in maturing hematopoietic cells. In the ensuing decades, the genetic basis of MDS has been revealed: it is now known that over 95% of MDS cases have an identifiable clonal genetic abnormality. In part for these reasons, MDS was renamed "myelodysplastic neoplasm" in the most recent WHO classification. Clonal myeloid proliferations in cytopenic patients that lack dysplasia (CCUS) are currently distinguished from MDS purely based on a lack of morphologic dysplasia identified by the pathologist reviewing the patient's bone marrow. However, the mutation profiles and clinical behavior of higher-risk CCUS cases overlaps that of lower-risk MDS, questioning whether the presence or absence of dysplasia that separates these entities is truly biologically relevant. Moreover, the assessment and quantification of dysplasia in MDS is subject to significant interobserver variability and also to the quality and processing of the submitted bone marrow sample. Dysplasia is not specific for MDS and is present in many cytopenic conditions that can mimic MDS clinically.

For these reasons, a MDS would be more appropriately diagnosed by its characteristic genetic profile, irrespective of the presence or absence of morphologic dysplasia. Identifying recurrent mutations and cytogenetic aberrations is more objective than assessing for dysplasia. Additionally, recent studies have identified distinct MDS genetic subtypes by artificial intelligence: these subtypes have unique clinical features and patient outcomes, transcending traditional historic morphologic MDS subtypes. Defining and classifying MDS based on its genetics rather than its morphology would both improve diagnostic reproducibility and offer potential therapeutic targets, optimizing future drug development. It would also open therapeutic options for cytopenic patients currently languishing in the CCUS category due to a lack of identifiable dysplasia. Current followup of MDS patients also relies largely on morphology (blast percentage); however, evaluating treatment responses the majority of MDS cases that lack increased blasts is challenging. The amelioration of MDS genetic abnormalities seen during treatment response offers a robust parameter that could be used to follow patients and guide treatment decisions.

In summary, the time is now ripe to adopt genetic criteria to diagnose and classify MDS. Morphology, particularly the blast percentage, undoubtedly remains prognostically relevant to stage and follow the disease. However, the biology of MDS and the features driving its recalcitrant cytopenia originate in its genome, demanding a definition and classification that is rooted in genetic features rather than morphology.

Yes

A.A. van de Loosdrecht

Diagnosis of cytopenic patients suspected of myelodysplastic neoplasms (MDS) can be challenging. Morphology is implemented in routine examination of peripheral blood and bone marrow smears to rapidly establish a clear-cut diagnosis to explain cytopenia and to coordinate the next steps of investigations including conventional cytogenetics, NGS and flow cytometry (FC). Next to the identification of molecular defined subsets in MDS [Komrokji RS et al. Lancet Haematol 2024;11:e826; Bernard E et al. Blood 2024;144:1617], the role of flow cytometry is recognized as complementary in an integrated diagnostic report [Van de Loosdrecht AA et al. Cytometry B Clin Cytom 2023;104:77]. In normal haematopoiesis, antigen expression on hematopoietic cells is tightly regulated; changes in expression patterns may therefore indicate dysplasia, the hallmark of MDS. Flow cytometry (FC) can identify aberrancies in antigen expression and maturation patterns not recognized by cytology FC and should be performed according to recommendations defined by the iMDS ELN flow cytometry working group, recently updated by Van der Velden et al. and Porwit et al. that include guidelines on sample preparation, instrument set-up and quality assessments, antibodies, and gating strategies [Cytometry B Clin Cytometry 2023;104;27, Cytometry B Clin Cytometry 2023;104:15]. Defined abnormalities can be counted in FC scoring systems to provide a means to determine the extent of dysregulation of the maturation patterns, i.e. dysplasia according to FC. Ideally, scores should enable a categorization of FC results from bone marrow assessments in cytopenic patients as "normal", "low probability of", or “high probability of” MDS [Cremers et al. Haematologica 2017;102:230, Oelschlaegel et al. Cytometry B Clin Cytom 2023;104:141]. A multicentre study identified a core set of 17 markers (CD45, CD34, CD117, HLA-DR, CD10, CD11b, CD13, CD16, CD15, CD14, CD33, CD64, CD123, CD7, CD19, CD56, and CD71) that enables identification of aberrancies in bone marrow cells independently related to the diagnosis of MDS by cytomorphology [Kern W et al., Cytometry B Clin Cytom 2023;104:51]. Veenstra C et al. confirmed the diagnostic validity of this marker set. They observed an overall diagnostic accuracy of 87% as compared to an integrated diagnostic approach at a cut-off of ≥3 aberrant markers. [HemaSphere 2025;9:e70075]. The sensitivity of the scoring system was 87% for lower risk and >90% for higher risk MDS cases (specificity 76%). Increased myeloid progenitor cells of ≥3 by FC may indicate MDS not only in cases with overt disease but also in cases with minimal dysplasia and confirmed in an independent cohort by Oelschlaegel U et al [Hemasphere 2025;9:e70235]. FC as a single technique is not sufficient for the diagnosis of MDS: FC results should always be evaluated as part of an integrated diagnostic work-up [Gisriel SD, et al. Arch Pathol Lab Med 2025;149:968]. Application of computational analysis and artificial intelligence to FC data, or combinations of FC data and other biological parameters, may support diagnosis-making, prognostication, and/or treatment decisions [Duetz C, et al. Haematologica 2023;108:2271; Duetz C, et al. Cytometry A 2021;99:814, Mocking TR et al. Leukemia 2025;39:2559].