



What is New in the 2016 Revision to WHO Classification of Myelodysplastic Syndromes?



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Abstract

The morphologic dysplasia manifested in any lineage(s) frequently does not correlate with the specific cytopenia(s) in individual MDS cases. For this reason, WHO revision for adult MDS classification in 2016 removes terms such as “refractory anemia” and “refractory cytopenia” and replaces them with “myelodysplastic syndrome” followed by the appropriate modifiers: single vs multilineage dysplasia, ring sideroblasts, excess blasts, or the del(5q) cytogenetic abnormality. In addition, the diagnostic criteria for MDS-RS is based on the detection of *SF3B1* mutations, the cytogenetic criteria for MDS with isolated del (5q) is modified, most cases of the erythroid/myeloid type of acute erythroleukemia are reclassified, and the familial link in some cases of MDS are recognized.

Abbreviations: MDS: myelodysplastic syndromes; HSC: hematopoietic stem cell; AML: acute myeloid leukemia; t-MDS: therapy-related MDS; ICUS: Idiopathic cytopenia(s) of undetermined significance; CHIP: clonal hematopoiesis of indeterminate potential; IPSS: International prognostic scoring system; WPSS: WHO prognostic scoring system; MDAS: MD Anderson score; LR-MDAS: MDAS for low-risk patients; AXSL1: Additional sex-comb-like transcriptional regulator-1; MDS-U: MDS, unclassifiable; MDS-RS: MDS with ring sideroblasts; FISH; fluorescent hybridization *in situ*; aCGH: array Comparative Genomic Hybridization.

Introduction

MDS are a heterogeneous group of clonal HSC malignancies characterized by ineffective hematopoiesis, peripheral blood cytopenias, and hypercellular bone marrow [1]. Approximately 30% of patients with MDS show progression to AML within a few months up to several years. Blast counts and cytogenetic abnormalities are the major determinants of the risk for malignant transformation [2].

The median age at diagnosis of MDS is ~70 years in the United States and Europe and is more than a decade younger in China and Eastern Europe, possibly due to environmental factors. Overall, there is a slight male predominance that may be partly related to occupational exposures. However, 5q-syndrome is more common in women than in men. Familial MDS with monosomy 7 has been reported [3]. The majority of patients affected by MDS are diagnosed during routine blood tests. Symptoms of MDS are often secondary to the peripheral cytopenias caused by the bone marrow failure [4].

There is no specific predisposing factor identifiable in most adult MDS patients other than advanced age. Idiopathic MDS represents 80% to 85% of cases. Secondary or t-MDS can be induced by alkylating agents, topoisomerase II inhibitors or

exposure to ionizing radiation. The latency period for t-MDS is typically 3-7 years after alkylating agent therapy and 1-3 years after epipodo phyllotoxins exposure. MDS can also result from exposure to DNA toxins, such as hydrocarbons [3].

The 2016 Revision to the WHO Classification of MDS [5]

- A. MDS with single lineage dysplasia
- B. MDS with ring sideroblasts (MDS-RS)
- C. MDS-RS and single lineage dysplasia
- D. MDS-RS and multilineage dysplasia
- E. MDS with multilineage dysplasia
- F. MDS with excess blasts
- G. MDS with isolated del(5q)
- H. MDS, unclassifiable
- I. Provisional entity: Refractory cytopenia of childhood

In the new revision, the diagnostic criteria for MDS with ring sideroblasts is based on the detection of *SF3B1* mutations, there

is modification of the cytogenetic criteria for MDS with isolated del(5q), reclassification of most cases of the erythroid/myeloid type of acute erythroleukemia, and recognition of the familial link in some cases of MDS [6].

MDS with isolated del (5q)

It may be diagnosed if there is 1 additional cytogenetic abnormality besides the del(5q), with the exception of monosomy 7 or del(7q). Evaluation for TP53 mutation is recommended to identify an adverse prognostic subgroup in this generally favourable prognosis MDS entity [5]. It has been shown that small subclones of hematopoietic cells that carry TP53 mutations occur at an early disease stage in approximately 20% of MDS patients with del (5q) and are associated with an increased risk of leukemic evolution and may be associated with lenalidomide resistance [1].

MDS-RS

SF3B1 mutations were found in >70% of patients whose disease is characterized by ring sideroblasts. The close association between SF3B1 mutation and the ring sideroblast phenotype is consistent with a causal link [1]. MDS-RS may be diagnosed if ring sideroblasts comprise as few as 5% of nucleated erythroid cells and SF3B1 mutation is identified, whereas at least 15% ring sideroblasts are required if a demonstrable SF3B1 mutation is lacking. MDS-RS cases are subdivided into cases with single lineage dysplasia (refractory anemia with ring sideroblasts previously) and cases with multilineage dysplasia (refractory cytopenia with multilineage dysplasia previously). MDS-RS cases lacking SF3B1 mutation appear to have an adverse prognosis compared with those with the mutation. The role of multilineage dysplasia vs the SF3B1 mutation in influencing outcome in MDS-RS remains controversial. The actual percentage of ring sideroblasts is not prognostically relevant [5].

MDS-U

It includes cases with single lineage dysplasia or isolated del (5q) and pancytopenia with all PB counts below the WHO thresholds [5]. Rare cases of familial MDS are associated with germ line mutations, by sequencing non-MDS patient tissue [5].

Pathogenesis of MDS

Abnormal responses to cytokine growth factors, impaired hematopoietic progenitor cell survival, excessive intramedullary apoptosis and defects in the marrow microenvironment have all been implicated [3].

Diagnosis

Peripheral blood and bone marrow findings

The WHO thresholds defining cytopenia remain hemoglobin <10 g/dL; platelets <100×10⁹/L; and absolute neutrophil count <1.8×10⁹/L. Rarely, MDS may be diagnosed with milder levels of cytopenia, but at least 1 cytopenia must be present [5]. The threshold to define dysplasia remains as 10% dysplastic

cells in any hematopoietic lineage. Some dysplastic changes, particularly the presence of micromegakaryocytes are relatively specific for myelodysplasia. In the updated classification, all nucleated BM cells, not just the “non erythroid cells.” are used for calculating blast percentage in erythroid/myeloid subtype of acute erythroid leukemia. This will reclassify most of these cases as MDS with excess blasts [5]. The presence of 1% blasts in the PB on at least 2 separate occasions with 5% BM blasts, defines MDS-U [5].

Genetics (cytogenetics, molecular genetics, and epigenetics)

Cytogenetics: Cytogenetic abnormalities are present in approximately 50% of de novo MDS and 80% of t-MDS cases [1]. Chromosomal monosomies and deletions are commonly observed with the most frequent sole abnormalities being del (5q), followed by trisomy 8, -Y, del (20q), and monosomy 7 [7]. Other recurrent deletions occurring in MDS include del (20q), del (17p), and del (11q) [1]. del (5q) remains the only cytogenetic or molecular genetic abnormality that defines a specific MDS subtype. The presence of +8, -Y, or del (20q) is not considered MDS defining in the absence of diagnostic morphologic features of MDS [5]. These cytogenetic abnormalities are often occurring in other myeloid malignancies, in addition, loss of chromosome Y can be found in healthy elderly males [7].

The presence of a complex karyotype (≥3 acquired chromosome abnormalities), abnormalities of chromosomes 5 and 7, or somatic TP53 mutation suggests the possibility of t-MDS. t-MDS secondary to alkylating agents or ionizing radiation exposure usually have abnormalities of chromosomes 5 and 7, whereas t-MDS secondary to epipodophyllotoxins exposure usually have abnormalities of chromosome 11q23. Translocations and inversions of 3q21/3q26 can arise after etoposide treatment and involve rearrangement of the MDS1-EVI1 (MECOM) genes; such patients often have a normal or elevated platelet count at the time of diagnosis and have a grim prognosis [3].

A complete BM karyotype remains a critical test in any newly diagnosed MDS case [5]. Nevertheless, non-informative karyotypes still concern in up to 20% of cases. The role of FISH in the diagnosis of MDS has not yet been well defined. Some studies demonstrated an overlap between conventional cytogenetics and FISH results, reserving the FISH analysis to those cases where karyotype failed. The addition of FISH (at least for chromosomes 5 and 7) can improve the definition of the risk score. aCGH use could be probably applied to cases with suboptimal response or failure. aCGH would be a potential method to detect cryptic relevant genomic markers and revealing chromosomal aberrations in 80% of cases defined as “normal” by conventional cytogenetic and FISH [4].

Genetics: Recurrent somatic mutations are observed in over 90% of patients with MDS and in about 10% of healthy individuals albeit with lower allele burdens of 10-20% [7].

These recurrently mutated genes are involved in epigenetic regulation (TET2, ASXL1, EZH2, DNMT3A, IDH1, IDH2), RNA splicing (SF3B1, SRSF2, U2AF35, ZRSR2), DNA repair (TP53), transcriptional regulation (RUNX1, BCOR, ETV6), signal transduction (CBL, NRAS, JAK2) and the cohesin complex (STAG2) [7]. The most common 12 mutated/deleted genes were TET2, SF3B1, and ASXL1 in >20% of patients; SRSF2, DNMT3A, and RUNX1 in >10% of cases; and U2AF1, ZRSR2, STAG2, TP53, EZH2, and CBL in >5% of cases [8].

Mutations in genes involved in RNA splicing or DNA methylation were found to occur in early MDS, whereas mutations in genes involved in chromatin modification and cell signalling tended to occur later [1]. Interestingly, spliceosome mutations show a strong tendency to co-occur with mutations of specific epigenetic modifiers in MDS, suggesting that abnormalities of these processes may cooperate to give the MDS phenotype. SRSF2 and ZRSR2 mutations are common in patients carrying mutations of the DNA methylation modifier TET2, SF3B1 mutations co-occur with mutation of the methyltransferase DNMT3A, and U2AF1 mutations have been associated with ASXL1 or TET2 mutations [1].

Recently, mutations of the spliceosome PRPF8 gene was found in approximately 1–4% of MDS patients and deletions of this gene was also observed in a similar percentage of patients. PRPF8 defects were strongly associated with the ring sideroblast phenotype [1]. The presence of chromothripsis involving chromosome 13 was a novel recurrent change in high-risk MDS patients. A key feature of chromothripsis is the occurrence of tens to hundreds of clustered genomic rearrangements usually in one or, in some instances, several chromosomes. This complex abnormality can affect an entire chromosome, a chromosome arm, or be confined to a single region of a chromosome [9]. The number of mutations increased linearly with age. Patients >50 years of age had TET2, SRSF2, and DNMT3A more commonly mutated compared to patients ≤50 years. In general, patients >50 years had more mutations in spliceosomal, epigenetic modifier, and RAS gene families [10].

Impact of Gene Mutations on Laboratory Findings

Mutations of ASXL1, RUNX1, and EZH2 have been significantly associated with reduced hemoglobin levels. Mutation of RUNX1, TP53, NRAS, ASXL1, and U2AF1 has been associated with thrombocytopenia, while SF3B1 mutations have been associated with a normal or increased platelet count. Mutations in ASXL1, SRSF2, CBL, RUNX1, WT1, IDH2, STAG2, and NRAS have all been shown to correlate with an increased percentage of bone marrow blasts [1].

In MDS with del (5q), haploin sufficiency of RPS14, have been implicated in inducing a P53-dependent block in erythroid proliferation and differentiation, whereas haploin sufficiency of two micro RNAs, mir145 and mir146a, that map within and adjacent to the CDR, respectively leads to dysmegakaryopoiesis [7] and thrombocytosis [1].

Clinical, Laboratory and Molecular Conditions at the Boundary of MDS

A. ICUS: patients must have persistent cytopenia in one or more lineage (hemoglobin <11 g/dL, neutrophil count <1.5 x 10⁹/L and platelet count <100 x 10⁹/L) for at least 6 months, not explained by any other disease and does not meet WHO-defined diagnostic criteria of MDS [11]. Their close observation is recommended. Many will be stable for a prolonged period; with or without complications from the cytopenias. Some patients will develop overt MDS or AML over time, whereas others may prove to have an alternative diagnosis [3].

B. CHIP is an acquired clonal mutation identical to those seen in MDS occurring in the hematopoietic cells of apparently healthy older individuals without MDS. The natural history of this condition is not yet fully understood. Some patients will subsequently develop MDS. Thus, the presence of MDS-associated somatic mutations alone in patients with unexplained cytopenia is not considered diagnostic of MDS [5].

Reactive Causes of Cytopenia and Dysplasia

Such as vitamin B12 and folate deficiency, HIV infection, copper deficiency, alcohol abuse, and medication effects (eg, antimetabolites such as methotrexate) can cause cytopenias and dysplastic changes in blood cells and need to be excluded [3].

Also consider that

A. Some ethnic groups may have a reference range for normal absolute neutrophil count that is lower than 1.8 x10⁹/L. Caution should be exercised in interpreting neutropenia if it is the only cytopenia [5].

B. Dysplasia in excess of 10% may occur in some normal individuals and even more frequently in non neoplastic causes of cytopenia particularly when the dysplasia is subtle and limited to 1 lineage [5].

C. Somatic, recurrent TET2 mutations have been found in normal elderly individuals with acquired clonal hematopoiesis. Moreover, recently TET2, DNMT3A, ASXL1, and SF3B1 mutations have been suggested to represent premalignant events that cause clonal hematopoietic expansion [1].

Prognosis: Prognostic Scores and Prognostic Impact of Cytogenetics and Molecular Genetics

Prognostic scores

Accurate assessment of prognosis becomes critical for therapeutic decision making [7]. The IPSS (1997) is still the most used prognostic tool, but a dynamic system score WPSS (2007) and the revised IPSS (R-IPSS) (2012) are also now available [4].

The IPSS uses blast percentage, karyotype, and number of cytopenias. Cytopenias were defined as mentioned above in diagnosis. Cytogenetic categories were: good (normal, -Y, del (20q), del (5q)), poor (chromosome 7 abnormalities, and

complex karyotype, and intermediate (all other abnormalities). The requirement for transfusions, WHO subtype, and IPSS cytogenetic categories were incorporated in the WPSS [7]. The IPSS-R takes into account the depth of cytopenias, blast percentage, and refined cytogenetic characterization which were: very good (-Y, del(11q), good (normal, del(5q), del(20q), del(12p)), intermediate (trisomy 8, del (7q)), poor (-7, inv3, complex karyotype with 3 abnormalities), and very poor (complex > 3 abnormalities) [7]. These three scores have limited application in clinical practice since they use de novo MDS patients having received supportive care alone [7].

In 2008, the MD Anderson group developed a score for t-MDS and previously treated MDS with disease-modifying therapy. The MDAS takes into consideration performance status, age, degree of anemia, thrombocytopenia, leukocytosis, bone marrow blast percentage, chromosome 7, or complex abnormalities and prior red cell or platelet transfusions. In addition, there is a separate LR-MDAS for low-risk patients that factors in age, hemoglobin, platelet count, bone marrow blast percentage, and poor cytogenetics [7].

The prognostic impact of cytogenetic deletion

The cytogenetic deletion maps of MDS (e.g., 5q-, 7q-, 20q-) provide circumstantial evidence for the presence of tumour suppressor genes. Haploinsufficiency of CUX1 is important in some patients with MDS with complete or partial loss of chromosome 7. CUX1 may exert tumour suppressor activity in myeloid cells through the regulation of genes involved in cell cycle control [1].

The prognostic impact of recurrent molecular mutations

The number and types of specific mutations are strongly associated with disease outcome in MDS. The addition of mutation data improves the prognostic value of existing risk-stratification schemes in MDS [5]. These molecular markers may also elucidate disease pathogenesis [8]. Mutations in TP53, EZH2, ETV6, RUNX1, ASXL1, DNMT3A, IDH1/2, BCL-6, SRSF2, NRAS, CBL, and STAG2 have been shown to be predictors of shortened survival. A particular study showed that mutations of EZH2, RUNX1, TP53, and ASXL1 were associated with inferior overall survival independent of the LR-MDAS. However, EZH2 mutations only retained prognostic significance in multivariable analysis [7].

There is no evidence that spliceosome mutations affect response to therapy but they are classically associated with a

better overall prognosis [12]. PRPF8 defects are associated with a more aggressive MDS phenotype [1]. TET2 mutations have been shown to predict response to DNMT inhibitor therapy in MDS [7]. In addition, another study identified TP53, TET2, or DNMT3A mutations as predictors of inferior survival post-transplant [7].

A 'poor risk' signature based on the expression of six genes, was defined and was associated with the risk of transformation from MDS to AML [1]. The clinical accuracy of GEP (on total bone marrow mononuclear cells) proved that only 50% of MDS samples were correctly classified, reflecting the marked heterogeneity of MDS [1].

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