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REVIEW

The International Consensus Classification of myelodysplastic syndromes and related entities

Robert P. Hasserjian[1] · Attilio Orazi[2] · Alberto Orfao[3] · Maria Rozman[4] · Sa A. Wang[5]

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Abstract

The International Consensus Classification (ICC) of myeloid neoplasms and acute leukemia has updated the classification of myelodysplastic syndromes (MDSs) and placed MDS in a broader group of clonal cytopenias that includes clonal cytopenia of undetermined significance (CCUS) and related entities. Although subject to some interobserver variability and lack of specificity, morphologic dysplasia remains the main feature that distinguishes MDS from other clonal cytopenias and defines MDS as a hematologic malignancy. The ICC has introduced some changes in the definition of MDS whereby some cases categorized as MDS based on cytogenetic abnormalities are now classified as CCUS, while *SF3B1* and multi-hit *TP53* mutations are now considered to be MDS-defining in a cytopenic patient. The ICC has also recognized several cytogenetic and molecular abnormalities that reclassify some cases of MDS with excess blasts as acute myeloid leukemia (AML) and has introduced a new MDS/AML entity that encompasses cases with 10–19% blasts that lie on the continuum between MDS and AML. Two new genetically defined categories of MDS have been introduced: MDS with mutated *SF3B1* and MDS with mutated *TP53*, the latter requiring bi-allelic aberrations in the *TP53* gene. The entity MDS, unclassifiable has been eliminated. These changes have resulted in an overall simplification of the MDS classification scheme from 8 separate entities (including 1 that was genetically defined) in the revised 4th edition WHO classification to 7 separate entities (including 3 that are genetically defined) in the ICC.

Keywords International Consensus Classification · Myelodysplastic syndromes · Clonal cytopenias · Myeloid neoplasms

Introduction

Myelodysplastic syndromes (MDSs) are a group of myeloid neoplasms characterized by clonal hematopoiesis and abnormal maturation of hematopoietic cells resulting in cytopenias. The initial stage in MDS development is the expansion of a mutated hematopoietic stem cell and its progeny within the bone marrow, termed clonal hematopoiesis (CH). Population studies have shown that CH in individuals with normal blood counts, termed clonal hematopoiesis of indeterminate potential (CHIP), increases with age [1, 2]. The expanded CH clone in some cases displays ineffective hematopoiesis that causes one or more blood cytopenias, and this combination of CH and otherwise unexplained cytopenia is termed clonal cytopenia of undetermined significance (CCUS). Since CCUS is a precursor lesion for MDS [3, 4], the 2022 International Consensus Classification (ICC) of myeloid neoplasms and acute leukemia recognizes CCUS and MDS together in a broad group of clonal cytopenias [5]. Morphologic dysplasia remains the main feature that distinguishes MDS from

✉ Robert P. Hasserjian
rhasserjian@partners.org

[1] Department of Pathology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Warren 244, Boston, MA 02114, USA

[2] Department of Pathology, Texas Tech University Health Sciences Center, El Paso, TX, USA

[3] Department of Medicine, Cytometry Service, Cancer Research Center (IBMCC-CSIC/USAL), Institute for Biomedical Research of Salamanca (IBSAL) and CIBERONC, University of Salamanca, Salamanca, Spain

[4] Hematopathology Section, Hospital Clinic de Barcelona, Barcelona, Spain

[5] Department of Hematopathology, MD Anderson Cancer Center, Houston, TX, USA

other clonal cytopenias and defines MDS as a hematologic malignancy [3]. However, the ICC has introduced several changes in the diagnostic boundaries of MDS: (1) an update to the genetic findings that can be used to diagnose MDS in the absence of significant morphologic dysplasia; (2) re-classification of some cases as "oligomonocytic" chronic myelomonocytic leukemia (CMML); (3) re-classification of some cases as acute myeloid leukemia (AML) based on certain specific genetic findings; and (4) the introduction of a new MDS/AML entity that encompasses cases with high blast percentage (10–19% blasts) that lie on the continuum between MDS and AML. In terms of individual MDS disease entities, the ICC has introduced two new genetically defined entities: *MDS with mutated SF3B1* (which encompasses most of the cases previously classified as MDS with ring sideroblasts) and *MDS with mutated TP53*. Given its independent prognostic significance in several studies, the distinction between single- and multi-lineage dysplasia is retained for cases that are not genetically defined and lack excess blasts (now called *MDS, not otherwise specified*, *MDS-NOS*); however, ring sideroblasts are no longer taken into account in MDS subclassification. Finally, the entity MDS, unclassifiable has been eliminated, as these cases are now placed in other MDS entities in the new classification. The MDS and MDS/AML entities of the ICC are listed in Table 1.

Pre-malignant clonal cytopenias

The expansion within the bone marrow (BM) and blood of a mutated hematopoietic clone underlies the etiology of most myeloid neoplasms, including MDS [6]. Pre-malignant clonal cytopenias are clonal hematopoietic proliferations associated with one or more peripheral blood (PB) cytopenias that are attributed to the abnormal clone (Table 2). Cytopenia in the context of clonal cytopenias is defined as an acquired and persistent anemia (hemoglobin < 12 g/dL in females and < 13 g/dL in males), neutropenia (absolute neutrophil count $< 1.8 \times 10^9$/L), and/or thrombocytopenia (platelets $< 150 \times 10^9$/L) that is not explained by another known or identifiable condition [7]. The clonality can be confirmed by detection of a somatic mutation (at variant allele frequency [VAF] of ≥ 2%) and or cytogenetic aberration. The related entity CHIP is defined by the presence of a somatic mutation in a myeloid neoplasm-associated gene (at VAF ≥ 2%) or a non-MDS-defining clonal cytogenetic aberration, in a patient with no known myeloid neoplasm and no unexplained cytopenia [8]. The incidence of CHIP increases with age and the most commonly affected genes are *DNMT3A*, *TET2*, and *ASXL1*, with a median VAF of 10% [1, 9]. Despite lacking (by definition) cytopenia, individuals with CHIP are at increased risk of developing myeloid neoplasia and also have increased morbidity and mortality due to other causes, particularly cardiovascular disease [10].

The main pre-malignant clonal cytopenia is CCUS, in which mutation in one or more myeloid-associated genes is accompanied by persistent (4 months or longer in duration) cytopenia(s). Any comorbid condition potentially causing the cytopenia(s) must be carefully excluded [3]. Importantly, microscopic examination of a BM sample is needed to categorize cytopenia(s) as CCUS, since the main distinguishing feature from MDS is the absence of morphologic dysplasia of BM hematopoietic elements and no increase in BM blasts. The risk of CCUS progressing to MDS and affecting patient survival is not uniform, but rather depends on several factors including the number of mutated genes, the VAF of the individual mutations, and the genes that are mutated. Specifically, spliceosome gene mutations as well as epigenetic modifier genes in combination with other mutations confer a high risk of progression to MDS and other myeloid neoplasms [4, 11]. In fact, some studies have shown that such higher-risk CCUS patients show prognosis comparable to patients diagnosed with lower risk MDS, despite the

Table 1 Myelodysplastic syndrome and MDS/AML entities*

MDS with mutated *SF3B1* (MDS-*SF3B1*)
MDS with del(5q) (MDS-del5q)
MDS not otherwise specified (MDS-NOS)
MDS-NOS, without dysplasia
MDS-NOS, with single lineage dysplasia (MDS-NOS-SLD)
MDS-NOS, with multilineage dysplasia (MDS-NOS-MLD)
MDS with excess blasts (MDS-EB)
MDS with mutated *TP53* (MDS-*TP53*)
MDS/AML
MDS/AML with myelodysplasia-related cytogenetic abnormalities
MDS/AML with myelodysplasia-related gene mutations
MDS/AML not otherwise specified
MDS/AML with mutated *TP53*

*Diagnostic qualifiers that can be applied after any MDS or MDS/AML entity include (1) therapy related; and/or (2) germline mutation or syndrome

Table 2 Pre-malignant clonal cytopenias

Name	Associated somatic mutations
Clonal cytopenia of undetermined significance (CCUS)	Various
Paroxysmal nocturnal hemoglobinuria (PNH)	*PIGA*
VEXAS syndrome	*UBA1*
Aplastic anemia with somatic mutation(s)	Various

absence of dysplasia [4, 12]. Further study is warranted to better define "high-risk" CCUS and its relationship to bona fide MDS; at this time, morphologic dysplasia is retained as the main discriminator between the pre-malignant condition CCUS and the hematologic malignancy MDS [11, 13].

Aside from CCUS, other unique clonal cytopenic syndromes include aplastic anemia (AA) with somatic mutation(s), paroxysmal nocturnal hemoglobinuria (PNH), and VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. While AA may be associated with various mutations, PNH and VEXAS are each associated with unique mutations. Over one third of AA patients display CH, with the most commonly affected genes (*BCOR*, *BCORL1*, and *PIGA*) being different from those of CCUS [14]. PNH is a clonal cytopenia characterized by somatic mutations in the *PIGA* gene in hematopoietic cells, which leads to abnormal loss of GPI-anchored proteins on the surface of erythrocytes and consequent hemolytic anemia [14, 15]. VEXAS syndrome is a unique autoinflammatory syndrome accompanied by anemia, autoimmune manifestations, and somatic mutation in the *UBA1* gene in hematopoietic cells, with characteristic vacuolization of erythroid and myeloid BM precursor cells [16]. Although VEXAS displays many features similar to MDS (ineffective erythropoiesis resulting in macrocytic anemia, CH, and morphologic abnormalities in BM precursors), the ICC recommends separating VEXAS from MDS given its unique multi-system features and extremely low incidence of progression to AML [17]. However, if significant dysplasia aside from erythroid and myeloid vacuolization is present, particularly when accompanied by acquisition of additional genetic aberrations, a diagnosis of MDS in the setting of VEXAS syndrome may be made [17]. Further study is needed to determine the role of morphologic dysplasia and additional genetic abnormalities besides the *UBA1* mutation in driving outcome of VEXAS patients. Similarly, both PNH and aplastic anemia may progress to MDS and conversely, a subset of MDS cases may be hypoplastic and/or display small PNH clones detected by flow cytometry. In such cases, the presence of significant dysplasia (including granulocytic or megakaryocytic dysplasia in PNH, which can demonstrate isolated erythroid dysplasia), excess blasts, and/or an MDS-defining genetic abnormality separates MDS from these non-MDS clonal cytopenias [18].

Cytopenias and CH may also be seen in patients following treatment for a myeloid neoplasm (most commonly AML) or a solid tumor, and in such cases, the clinical and biological implications may be different from CHIP or CCUS occurring in patients lacking a history of neoplasia [19]. In particular, the presence of CH in cancer patients exposed to cytotoxic chemotherapy and/or radiotherapy is a risk factor for the development of therapy-related MDS and AML, with highest risk conferred by *TP53* and *PPM1D* mutations [20, 21]. Conversely, CH detected in AML patients post-chemotherapy, especially so-called DTA (*DNMT3A*, *TET2*, and *ASXL1*) mutations, may not necessarily confer adverse outcome or increased risk of relapse, although further study and longer followup is needed [19, 22].

A threshold VAF of $\geq 2\%$ is recommended to define CCUS and other pre-malignant clonal cytopenias, recognizing that certain mutations and higher VAF are associated with higher risk of progression to MDS [4]. However, mutations at VAF of $< 20\%$ should be interpreted with caution, since mutated CCUS clones are thought to exert a cytopenic effect by diminishing normal hematopoiesis, and this effect would be unlikely for a clone size of $< 40\%$ (corresponding to a VAF of $< 20\%$ for a heterozygous mutation) [23]. In such patients, a possible secondary cause of the cytopenia should be rigorously sought before labeling the patient as having CCUS. When considering the VAF as a reflection of the hematopoietic clone, it should be noted that VAF is only an estimation of the mutation burden, which may be affected by sample quality (presence of myeloid hematopoietic cells versus lymphocytes and non-hematopoietic cells) and loss-of-heterozygosity (LOH) of the mutated gene.

Myelodysplastic syndromes: minimal defining criteria

Although there is no formal requirement for cytopenia duration in MDS, there should be clinical evidence that the cytopenia(s) is chronic (typically 4 months or longer) and is not explained by an exogenous factor or comorbid condition. The minimal threshold for defining dysplasia remains at 10% for all lineages. However, for megakaryocytes, this cutoff may not be sufficiently specific when including dysplastic changes other than micromegakaryocytes [24, 25]. Therefore, while a minimum of 10% micromegakaryocytes is sufficient to establish significant megakaryocytic dysplasia, a higher threshold (30% or 40%) may be more appropriate when including other types of megakaryocytic dysplasia, such as normal sized forms with non-lobated round nuclei or multiple separated nuclear lobes, or megakaryocytes with "naked" nuclei [26]. Micromegakaryocytes are defined as small megakaryocytes with a cell size approximating that of a promyelocyte (Fig. 1). They can be identified in the BM aspirate smear and in the biopsy, particularly when applying a megakaryocyte immunostain such as CD61 (Fig. 1). Close attention to identifying morphologic dysplasia in putative MDS cases lacking an MDS-defining genetic abnormality remains critical even in the current era of next-generation sequencing (NGS). Although a somatic genetic aberration is identifiable in over 90% of MDS cases when combining targeted NGS panels with conventional karyotype, a diagnosis of MDS can still be made in the 5–10% of cases lacking a clonal genetic marker in the presence of qualifying dysplasia

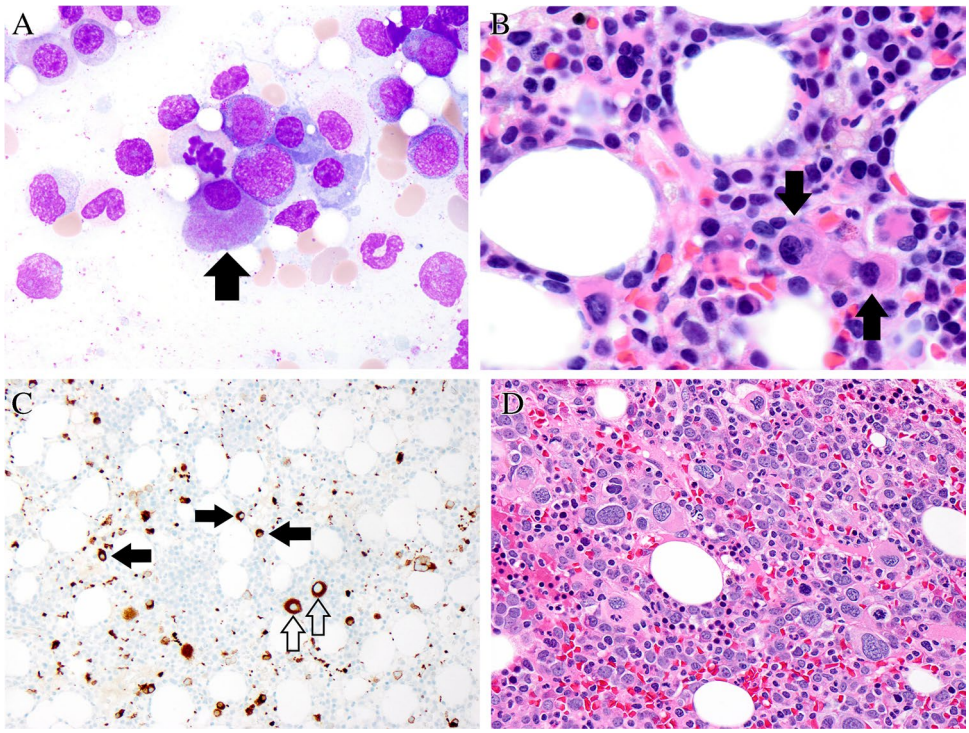

Fig. 1 Illustration of megakaryocytic dysplasia in cases of MDS, including micromegakaryocytes, which are the most specific dysmegakaryopoietic feature. **A** Bone marrow aspirate smear showing a micromegakaryocyte (arrow), which is of similar size to adjacent promyelocytes and approaches the size of a plasma cell; however, the finely granulated pale basophilic cytoplasm and dispersed (rather than condensed "clock-face") nuclear chromatin identify it as a megakaryocyte (Wright-Giemsa). **B** Bone marrow biopsy showing two micromegakaryocytes (arrows), as well as a dysplastic multinucleated megakaryocyte to the right (H&E). **C** CD61 immunostain of bone marrow biopsy showing micromegakaryocytes (solid black arrows) as well as small non-lobated megakaryocytes (hollow vertical arrows); the latter are dysplastic, but are too large to qualify as micromegakaryocytes. **D** Bone marrow biopsy showing striking dysmegakaryopoiesis with numerous forms showing non-lobated nuclei. Although most of these forms are too large to qualify as micromegakaryocytes, they comprise well above 40% of all megakaryocytes and thus establish the presence of dysmegakaryopoiesis (H&E)

and persistent cytopenia. These MDS cases with no identifiable somatic mutations or cytogenetic aberrations display similar behavior to MDS with identifiable pathogenic mutations, suggesting that the failure to identify a mutated clone likely reflects limitations in current clinical genetic assays rather than a biologically distinct disease [27]. However, care must be taken to consider secondary causes of dysplasia and cytopenia and avoid overcalling MDS [28, 29]. The presence of MDS-type mutations (particularly when present at high VAF, at least 10% and typically over 20%) on NGS or cytogenetic aberrations on karyotype can be helpful in confirming that any dysplasia in patients who have comorbid conditions that can cause cytopenia and dysplasia is genuine [28].

In the prior revised 4th edition WHO classification, a number of cytogenetic abnormalities in the context of persistent cytopenia were considered to be MDS defining, even in the absence of sufficient dysplasia or increased blasts, and such cases were categorized as MDS, unclassifiable (MDS-U). This list of MDS-defining genetic abnormalities has been updated and simplified to del(5q), − 7, del(7q), or complex karyotype (≥ 3 independent cytogenetic abnormalities, except -Y) on conventional karyotype of BM, and multihit *TP53* or *SF3B1* mutation (at VAF of ≥ 10%) on molecular studies. *SF3B1* and *TP53* mutations in CCUS (i.e., cytopenic patients lacking sufficient dysplasia to diagnose MDS based on morphologic criteria) share biologic features to MDS with the same mutations, and exhibit similar overall survival to MDS cases with comparable mutations [11]. Thus, the Clinical Advisory Committee of the ICC favored including these mutations among the MDS-defining genetic features. The other previously MDS-defining cytogenetic abnormalities (Table 6.03 in [30]) are now considered within CCUS because their biological and prognostic implications in cases lacking morphologic dysplasia are uncertain [31]. In the absence of dysplasia, previous MDS-U cases are now classified either in their specific genetic category—MDS with mutated *SF3B1*, MDS with mutated *TP53*, or MDS with del(5q)—or, in the case of chromosome 7 abnormalities or complex karyotype—are classified as MDS-NOS, without dysplasia (discussed below). MDS in children (patients < 18 years old) has biologic features that are

distinct from MDS in adults [32, 33], and thus refractory cytopenia of childhood (RCC) and other pediatric MDS are discussed in a separate article in this series.

Myelodysplastic syndromes: diagnostic boundaries with other myeloid neoplasms including acute myeloid leukemia

Persistent leukocytosis (WBC $\geq 13.0 \times 10^9$/L, not explained by lymphocytosis or another comorbid condition), thrombocytosis (platelets $\geq 450 \times 10^9$/L, except in cases meeting criteria for MDS with del(5q) or with inv(3)/t(3;3)) or monocytosis (monocytes $\geq 10\%$ of leukocytes and absolute monocyte count $\geq 0.5 \times 10^9$/L) at the time of initial diagnosis exclude MDS and warrant classification as MDS/myeloproliferative neoplasm (MDS/MPN) or MPN. These exclusionary features remain unchanged from the revised 4th edition WHO classification with the exception of a lower absolute (0.5×10^9/L) monocyte count in the context of at least 10% PB monocytes defining CMML. This results in some cases previously classified as MDS (with $0.5–0.9 \times 10^9$/L PB monocytes) now being classified as CMML [34–36]. Most such cases of so-called oligomonocytic CMML will display a characteristic mutation pattern (*TET2*, *ASXL1*, and/or *SRSF2* mutations, often in combination). Moreover, both the relative and absolute monocytosis should be shown to persist on multiple occasions upon followup, since MDS patients may develop a superimposed transient monocytosis due to an infection or inflammatory condition.

Although exclusionary at the time of initial diagnosis, the secondary development of leukocytosis, thrombocytosis, or monocytosis in an established MDS case generally does not warrant reclassification as MDS/MPN. Such cases should be designated as MDS, subtyped according to the specific MDS category, and noted to have neutrophilic, thrombocytotic, or monocytic progression. Unlike the revised 4th edition WHO classification, cases of MDS with *SF3B1* mutation that later develop thrombocytosis (with or without a *JAK2* mutation) are also no longer reclassified as MDS/MPN. Cases resembling bona fide CMML or, rarely, atypical chronic myeloid leukemia may develop in patients previously diagnosed with MDS; further study is needed to distinguish between MDS progression and true conversion to an MDS/MPN in these rare instances [37–39].

There is an increasing recognition that the blast threshold of 20% that has separated MDS from AML since the 3rd edition WHO classification in 2001 may not be optimal in defining these two disease categories that have different management approaches [40, 41]. Three cytogenetic aberrations—*PML::RARA*, *RUNX1::RUNXT1*, and *CBFB::MYH11*—are already considered to be AML defining given that patients with these myeloid neoplasms rapidly progress to overt AML when they present with < 20% blasts and are effectively managed by up front AML-type therapy [42]. Recent data suggest that *NPM1* mutations and *KMT2A* rearrangements are also AML-defining genetic alterations that lead to rapid disease progression even if they present initially with < 20% blasts [43–46]. Moreover, patients with *NPM1* mutations and < 20% blasts may benefit from being managed with intensive therapy, similar to patients presenting with ≥ 20% blasts [44, 45]. Several other recurrent gene rearrangements, including *MECOM* rearrangements and *DEK::NUP214*, are associated with aggressive myeloid neoplasms that behave similarly whether presenting as MDS (with < 20% blasts) or AML (with ≥ 20% blasts) [47, 48]. Accordingly, *NPM1* and somatic *CEBPA* in-frame bZIP mutation as well as several specific gene rearrangements are now considered to be AML defining, and mandate classification as AML even if the PB and BM blast percentage is < 20% [49]. Given that rare cases with these AML-defining genetic aberrations may present with no increase in blasts and some display indolent behavior [50, 51], the ICC recommends that these AML-defining genetics only apply to cases with at least 10% BM or PB blasts. Cases with *PML::RARA*, *RUNX1::RUNXT1*, or *CBFB::MYH11* rearrangements and < 10% blasts are exceedingly rare. In such cases, careful attention should be paid to including blast equivalents (promonocytes as well as promyelocytes in the case of *PML::RARA*) in the blast count and confirming the cytogenetic findings, particularly if detected at a low level [42]. Many of these cases likely represent early AML and could be treated as such if clinically indicated, particularly in the absence of MDS morphologic features [52]. Conversely, cytopenic patients with significant morphologic dysplasia, < 10% blasts, and any of the other AML-associated genetic findings should continue to be classified as MDS until further data can be accumulated as to the clinical behavior and optimal treatment approach of these rare cases.

Aside from the abovementioned AML-defining genetic aberrations, blasts in cases along the MDS to AML spectrum appear to behave as a continuous variable with respect to disease clinical behavior and phenotype. This is underscored by conversion of the previously categorical blast variable (0–2%, 3–4%, 5–10%, > 10%) in the Revised International Prognostic Scoring System (IPSS-R) to a continuous variable in the Molecular International Prognostic Scoring System (IPSS-M) [53]. The transformation of MDS to AML reflects a progressive increase in blasts due to impaired maturation of the malignant clone, and thus MDS and many AML subtypes (excluding those with AML-defining genetic abnormalities, discussed above) form a biologic continuum rather than representing two distinct diseases separated by an arbitrary blast cutoff [40, 41, 54, 55]. Blast counting in the BM, while relatively reproducible compared to distinction between single and multilineage dysplasia [56], can be

subjective and is affected by pre-analytic variables such as hemodilution and the quality of the aspirate smears. Estimation of the blast count based on CD34 staining on the BM core biopsy can be helpful, particularly when the aspirate is hemodilute or subject to other artifacts [57]. It is recommended to use the blast percentage based on CD34 staining of the biopsy if it is higher than the aspirate blast count, since this likely more accurately reflects the true BM blast percentage (Fig. 2).

To acknowledge this biologic continuum between MDS and AML and imprecision in counting blasts around the rigid 20% threshold that has historically separated these entities, myeloid neoplasms previously classified as MDS with excess blasts-2 (MDS-EB2) with 10–19% blasts in the PB and/or BM are placed in a new disease entity *MDS/AML* (Table 3). While some adult patients with myeloid neoplasms and 10–19% blasts can be treated effectively with intensive AML-type chemotherapy [41, 58, 59], in the future, treatment of individual patients in this MDS/AML group will likely be dictated by genetic, biological, and patient-related factors rather than an arbitrary blast percentage [41]. Recent studies have shown that mutations in signaling genes (such as *NRAS*, *PTPN11*, *FLT3*, and *CBL*) and *IDH1* and *IDH2* mutations may drive the progression of MDS to AML and the presence of such mutations could inform the management patients with MDS/AML [60, 61]. Stable versus rapid progression of the blast percentage and cytopenias during clinical followup also may also be informative in driving treatment decisions of patients with MDS/AML (10–19% blasts) and oligoblastic AML (20–29% blasts) [62]. In the meantime, this change will allow patients with MDS/AML to be eligible for both MDS and AML trials, facilitating their optimal management. Pediatric patients with 10–19% blasts (with the exception of those with AML-defining genetic aberrations, as discussed above) continue to be classified as MDS-EB, as these patients have features that are distinct from adult MDS/AML. It is recommended that patients with MDS/AML who are treated as AML be classified according to the genetic AML categories, i.e., as *MDS/AML with myelodysplasia-related cytogenetic abnormalities*, *MDS/AML with myelodysplasia-related gene mutations*, and *MDS/AML-NOS* [5, 49] (Table 3). As discussed below, cases with 10–19% blasts and *TP53* mutation should be classified as *MDS/AML with mutated TP53*.

Table 3 Diagnostic criteria for MDS/AML*

Feature	Requirements
Blood counts	At least one cytopenia; no cytoses**
Morphology	Dysplasia is typically seen, but not required
Blasts/Auer rods	10–19% BM or 10–19% PB, with or without Auer rods
Cytogenetics	No AML-defining karyotype abnormality***
Molecular genetics	No *NPM1* or *CEBPA* in-frame bZIP mutation
WHO revised 4th edition equivalents	Most cases of MDS-EB2

*MDS/AML may be further subclassified as MDS/AML with myelodysplasia-related gene mutations, MDS/AML with myelodysplasia-related cytogenetics, MDS/AML-NOS, or MDS/AML with mutated *TP53* (mono-allelic or multi-hit).

**Cytoses: sustained white blood count $\geq 13\times10^9$/L, monocytosis ($\geq 0.5\times10^9$/L and $\geq 10\%$ of leukocytes), or platelets $\geq 450\times10^9$/L.

***See separate article on AML in this series for the list of AML-defining karyotype abnormalities

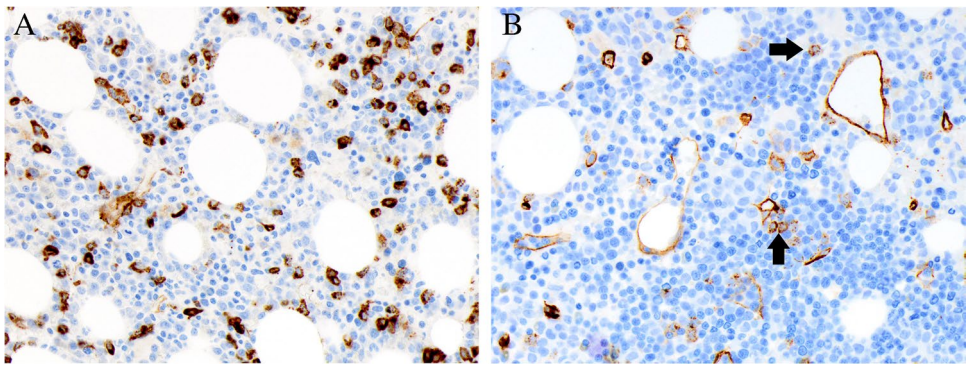

Fig. 2 Use of CD34 immunostaining in MDS cases to highlight blasts in trephine biopsy. **A** A case of a patient presenting with pancytopenia in which the bone marrow aspirate blast count was 7%, consistent with MDS-EB. CD34 immunostain on the core biopsy shows CD34 + blast cells comprising 5–10% of the cellularity, concordant with the aspirate blast count. **B** A case of MDS-NOS-SLD, showing strong CD34 staining of small blood vessels, but only rare blasts (arrows). The latter are distinguishable from small vessels by the presence of a central nucleus and sightly granular rather than solid, intense staining

Myelodysplastic syndromes: lower risk subtypes

The overall ICC classification of MDS retains the important division of those without and with excess blasts. Among cases without excess blasts, MDS with isolated del(5q) in the revised 4th edition WHO classification is essentially unchanged, although the name has been simplified to *MDS with del(5q)* with the understanding that the del(5q) must be isolated or accompanied by only one other cytogenetic aberration except − 7 or del(7q) (Table 4). Mono-allelic *TP53* mutation is allowed in MDS with del(5q) and, although it appears to convey a reduced likelihood of response to lenalidomide [63], it is not associated with the same dismal prognosis as multi-hit *TP53* mutation [64]. Thus, a multi-hit *TP53* mutation excludes classification as MDS with del(5q) and mandates classification as MDS with mutated *TP53*. Pancytopenia is now allowed in MDS del(5q), and 1% PB blasts is also allowed if only detected on one occasion. However, as in the revised 4th edition WHO classification, a PB blast count of 2% or higher or the presence of Auer rods in blasts excludes a diagnosis of MDS with del(5q) and mandates classification as MDS-EB.

The category MDS with ring sideroblasts (MDS-RS) has been dissolved: the new entity *MDS with SF3B1 mutation* now encompasses many, but not all of the cases previously classified as MDS-RS (Table 5). *SF3B1* is the only gene to confer a favorable prognosis for MDS patients [65]. Moreover, unsupervised clustering analysis identifies *SF3B1*-mutated cases as a major MDS genetic disease group [66, 67] and this splicing gene mutation results in a high number of differentially expressed genes compared to other MDS-associated mutations [68–70]. The *SF3B1* mutation VAF is required to be 10% or higher. The presence of excess blasts as well as several genetic features—del(5q), − 7/del(7q), inv(3) or abnormal 3q26, complex karyotype, *TP53*, or *RUNX1* mutations—negates the favorable effect of *SF3B1* mutation and disqualifies a case from the category of MDS with mutated *SF3B1* [71]. Ring sideroblasts do not appear to have prognostic significance once *SF3B1* mutation has been taken into account [71, 72], and thus ring sideroblasts no longer define any specific MDS category in the ICC. Conversely, a diagnosis of MDS with mutated *SF3B1* may be made even in the absence of ring sideroblasts, although these cases are rare [71]. It is still recommended to perform an iron stain on a BM aspirate smear in any putative MDS

Table 4 Diagnostic criteria for MDS with del(5q)

Feature	Requirements
Blood counts	At least one cytopenia; no leukocytosis or monocytosis*
Morphology	Dysplasia (particularly in the megakaryocytic lineage) is usually present, but not required
Blasts/Auer rods	< 5% BM, < 2% PB No Auer rods
Cytogenetics	Del(5q) with up to 1 additional abnormality No − 7 or del(7q)
Molecular genetics	No multi-hit *TP53* mutation (VAF ≥ 10%)
WHO revised 4th edition equivalents	MDS with isolated del(5q)

*Sustained white blood count $\geq 13 \times 10^9$/L or monocytes $\geq 0.5 \times 10^9$/L and ≥ 10% of leukocytes

Table 5 Diagnostic criteria for MDS with mutated *SF3B1*

Feature	Requirements
Blood counts	At least one cytopenia; no cytoses*
Morphology	Dysplasia (particularly in the erythroid lineage) and ring sideroblasts are usually present, but not required
Blasts/Auer rods	< 5% BM, < 2% PB No Auer rods
Cytogenetics	No del(5q), − 7/del(7q), abnormal 3q26.2, or complex karyotype**
Molecular genetics	*SF3B1* mutation (VAF ≥ 10%) No multi-hit *TP53* or *RUNX1* mutation
WHO revised 4th edition equivalents	Most cases of MDS-RS-SLD/MLD, rare cases of MDS-SLD/MLD

*Cytoses: sustained white blood count $\geq 13 \times 10^9$/L, monocytosis ($\geq 0.5 \times 10^9$/L and ≥ 10% of leukocytes), or platelets $\geq 450 \times 10^9$/L

**Complex karyotype defined as 3 independent cytogenetic abnormalities (excluding -Y)

case, since ring sideroblasts by definition represent dysplastic erythroid cells and can help confirm erythroid dysplasia in establishing an MDS diagnosis, provided that non-neoplastic causes of ring sideroblasts, such as alcohol, drugs, and some inherited conditions, are excluded. Additionally, the presence of ring sideroblasts in an MDS case increases the likelihood of MDS with mutated *SF3B1*.

MDS, not otherwise specified (*MDS-NOS*) encompasses cases previously called MDS with single lineage dysplasia and MDS with multilineage dysplasia, as well as MDS with ring sideroblasts that lack *SF3B1* mutation or have *SF3B1* mutation together with any of the genetic exclusionary features (Table 6). Although distinction between single lineage (SLD) versus multilineage (MLD) dysplasia is subject to interobserver reproducibility [73], this distinction has been retained as *MDS-NOS-SLD* and *MDS-NOS-MLD* subtypes. Multiple studies have shown that MDS cases with MLD have an inferior prognosis and distinct genetic profiles compared to cases with dysplasia limited to a single lineage [71, 74, 75], and the prognostic significance remains even in the multivariable models that include the effect of gene mutations [76]. Thus, maintenance of the SLD versus MLD distinction (with the exception of MDS with mutated *SF3B1*, del(5q), and mutated *TP53*, see above) is still felt to be warranted at the current time. Unlike the prior classification, pancytopenia is now allowed in MDS-NOS-SLD: while the number and depth of cytopenias does influence the prognosis of low-blast MDS cases, these are already taken into account in the IPSS-R and IPSS-M risk stratification schemes [53, 77] and thus are no longer relevant for actual MDS disease classification. MDS-NOS also includes the rare cases previously called MDS, unclassifiable due to an MDS-defining cytogenetic abnormality without qualifying (≥ 10%) morphologic dysplasia, and these are termed *MDS-NOS, without dysplasia*. Cytopenic patients with non-MDS-defining cytogenetic abnormalities (discussed above) and lacking qualifying dysplasia are categorized as CCUS.

Lower-risk MDS thus now comprises three disease entities: MDS with mutated *SF3B1*, MDS with del(5q), and MDS, NOS (the latter subclassified as MDS-NOS-SLD, MDS-NOS-MLD, and MDS-NOS, without dysplasia). Importantly, the presence of a multi-hit *TP53* mutation excludes any of the above entities and such cases are classified as MDS with mutated *TP53* irrespective of the presence or absence of excess blasts. In the near future, genetic clustering analysis will likely aid in establishing additional genetic subgroups within MDS-NOS [66, 67]. It is important to note that MDS is not a static disease: lower risk MDS subtypes may progress to MDS-EB, MDS/AML, or AML when blasts in the PB or BM increase above the designated thresholds, and in such cases the progression from the lower-risk MDS entity should be noted in the report. Lower-risk MDS subtypes may also acquire multi-hit *TP53* mutation and then should be diagnosed as progression to MDS with mutated *TP53*.

Myelodysplastic syndromes: higher risk subtypes

MDS with excess blasts (*MDS-EB*) is separated from lower-risk MDS subtypes by the presence of at least 5% myeloid blasts in the BM and/or at least 2% blasts in the PB, or the presence of any Auer rods in blasts (Table 7). Given the elimination of the category of MDS, unclassifiable, the presence of 1% PB blasts on one occasion is acceptable in any of the MDS subtypes without excess blasts discussed above. However, these patients should be followed closely and should be classified as MDS-EB if PB blasts of 1% or

Table 6 Diagnostic criteria for MDS-NOS

Feature	Requirements
Blood counts	At least one cytopenia; no cytoses*
Morphology	MDS-NOS, without dysplasia: < 10% dysplastic forms in any lineage MDS-NOS-SLD: ≥ 10% dysplastic forms in 1 hematopoietic lineage MDS-NOS-MLD: ≥ 10% dysplastic forms in 2 or 3 hematopoietic lineages
Blasts/Auer rods	< 5% BM, < 2% PB No Auer rods
Cytogenetics	MDS-NOS, without dysplasia: − 7/del(7q) or complex karyotype** MDS-NOS-SLD/MLD: does not meet cytogenetic criteria for MDS-del(5q)
Molecular genetics	No multi-hit *TP53* mutation (VAF ≥ 10%) or *SF3B1* mutation (VAF ≥ 10%) without *RUNX1* mutation
WHO revised 4th edition equivalents	Most cases of MDS-SLD/MLD, some cases of MDS, unclassifiable, and some cases of MDS-RS-SLD/MLD

*Cytoses: sustained white blood count ≥ 13×10^9/L, monocytosis (≥ 0.5×10^9/L and ≥ 10% of leukocytes), or platelets ≥ 450×10^9/L, except thrombocytosis is allowed in the setting of inv(3)/t(3;3)

**Complex karyotype defined as 3 independent cytogenetic abnormalities (excluding -Y)

Table 7 Diagnostic criteria for MDS-EB

Feature	Requirements
Blood counts	At least one cytopenia; no cytoses*
Morphology	Dysplasia is typically seen, but not required
Blasts/Auer rods	5–9% BM or 2–9% PB or Auer rods
Cytogenetics	Any
Molecular genetics	No multi-hit *TP53* mutation (VAF ≥ 10%)
WHO revised 4th edition equivalents	Most cases of MDS-EB1, some cases of MDS-EB2 (with 5–9% PB blasts or Auer rods)

*Cytoses: sustained white blood count $\geq 13\times10^9$/L, monocytosis ($\geq 0.5\times10^9$/L and ≥ 10% of leukocytes), or platelets $\geq 450\times10^9$/L, except thrombocytosis is allowed in the setting of inv(3)/t(3;3)

higher are confirmed at a later date and in the absence of any secondary cause for increased blasts, such as infection, growth factor, or recovery from treatment [78]. With the introduction of the new MDS/AML category (discussed below), there is now only one MDS-EB subtype. MDS-EB encompasses all prior MDS-EB1 cases and the subsets of MDS-EB2 cases with Auer rods or 5–9% blasts in the PB (and < 10% blasts in the BM). The presence of excess blasts supersedes any of the above MDS subtypes, except MDS with mutated *TP53*.

A new high-risk entity *MDS with mutated TP53* has been created that includes cases with both low (< 5%) and increased (6–9%) blasts and multi-hit (i.e., bi-allelic) *TP53* mutation (Table 8 and Fig. 3). Unlike other MDS cases, blast percentage does not appear to exert a prognostic effect in the setting of multi-hit *TP53* [64, 79]. MDS with mutated *TP53* is considered together in a disease group with MDS/AML and AML with mutated *TP53* (including pure erythroid leukemia) due to their overall similar aggressive behavior the warrants a more unified treatment strategy across the blast spectrum [59, 79]. However, for classification purposes, cases should continue to be diagnosed as MDS, MDS/AML, or AML with mutated *TP53*, following the BM and PB blast percentage thresholds defining these three diseases. This category includes cases of *TP53*-mutated MDS that are erythroid-rich but do not meet criteria for pure erythroid leukemia due to insufficient erythroid elements or pronormoblasts [80]. In one recent series of *TP53*-mutated MDS (that included both mono-allelic and multi-hit cases), about half of the cases lacked excess blasts and the vast majority of these showed multilineage dysplasia [81]. *TP53* mutation can be suspected in MDS based on intense nuclear staining of at least 2% of cells in the bone marrow trephine biopsy [82, 83], although these results should be confirmed by mutation testing and to assess for multi-hit status as appropriate (Fig. 3).

MDS with mutated *TP53* requires multiple hits to the *TP53* gene ("multi-hit" or "bi-allelic"), which can be confirmed by the presence of two or more distinct *TP53* mutations (each at VAF ≥ 10%), or a single *TP53* mutation (VAF ≥ 10%) associated with either: (1) a cytogenetic deletion involving the *TP53* locus at 17p; (2) a VAF of > 50%; or (3) copy number-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus [59, 84, 85]. In the absence of LOH information, the presence of a single *TP53* mutation at VAF ≥ 10% in the context of any complex karyotype is considered equivalent to a multi-hit *TP53* [59, 84]. Recent data suggest some differences in the pathogenicity and impact on disease outcome of specific *TP53* mutations, but it remains to be determined if a mutation phenotype score should be incorporated into risk stratification of *TP53*-mutated cases [81, 86].

It should be noted that complex karyotype alone without a *TP53* mutation, even in the presence of 17p deletion, does not qualify for this category, as these cases have a better prognosis compared to *TP53*-mutated MDS [79, 87]. Mono-allelic *TP53* mutations in MDS have different biology from cases with multi-hit *TP53* and are not included within the MDS with mutated *TP53* category. However, mono-allelic mutated *TP53* appears to confer a similarly poor prognosis

Table 8 Diagnostic criteria for MDS with mutated *TP53*

Feature	Requirements
Blood counts	At least one cytopenia; no cytoses*
Morphology	Dysplasia is typically seen, but not required
Blasts/Auer rods	0–9% BM or 0–9% PB, with or without Auer rods
Cytogenetics	If only a single *TP53* mutation with VAF 10–49% is present and LOH information is not available, a complex karyotype** and/or 17p deletion on karyotype is required
Molecular genetics	Either two or more *TP53* mutations (each with VAF ≥ 10%) or a single *TP53* mutation with VAF > 50% and/or VAF ≥ 10% together with LOH at the 17p *TP53* locus
WHO revised 4th edition equivalents	Many cases of MDS-EB1, some cases of MDS-EB2 with 5–9% PB blasts or Auer rods, some cases of MDS-MLD, rare cases of MDS-SLD and MDS-RS, and very rare cases of MDS with isolated del(5q)

*Cytoses: sustained white blood count $\geq 13\times10^9$/L, monocytosis ($\geq 0.5\times10^9$/L and ≥ 10% of leukocytes), or platelets $\geq 450\times10^9$/L

**Complex karyotype defined as 3 independent cytogenetic aberrations (excluding -Y)

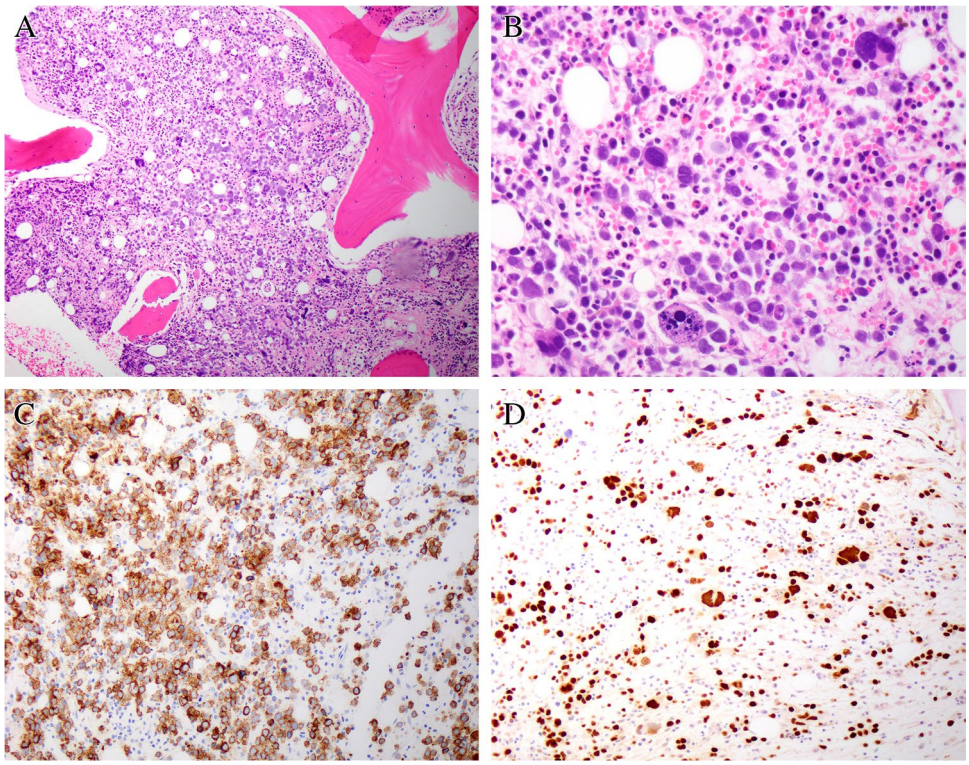

Fig. 3 A case of MDS with mutated *TP53*, therapy-related in a 41 year-old man presenting with pancytopenia 3 years after chemotherapy for a germ cell tumor; a BM aspirate was not obtainable due to "dry tap." **A** Low power view of the BM core biopsy shows marked hypercellularity with many immature large forms (H&E). **B** On higher power, there are many pronormoblasts and small, dysplastic megakaryocytes, but also maturing erythroid and granulocytic elements (H&E). **C** CD71 immunostain confirms that many cells in the marrow are erythroids, but these are insufficient in number (< 80%) to warrant a diagnosis of pure erythroid leukemia and also exhibit left-shifted, but intact maturation. **D** An immunostain for p53 protein highlights strong expression in many of the erythroid cells and megakaryocytes, correlating with the subsequent genetic finding of a multi-hit *TP53* mutation

as multi-hit *TP53* in cases with increased blasts (≥ 10%), and thus mono-allelic *TP53* mutations are allowed in MDS/AML with mutated *TP53* [59] (Table 3).

Diagnostic qualifiers

In previous classifications, MDS that developed in patients previously treated with cytotoxic chemotherapy and/or radiation therapy with large fields of BM exposure were classified as therapy-related myeloid neoplasms (t-MNs), together with therapy-related MDS/MPN and AML. However, recent data that incorporate genetic characterization of t-MN have shown that t-MDS and t-AML are different and their behavior is influenced by their underlying genetic features [20, 88, 89]. In fact, current risk stratification schemes like the IPSS-R and IPSS-M highlight the heterogeneous behavior of therapy-related MDS and indicate that these cases warrant further subclassification [53, 89, 90]. For these reasons, "therapy-related" no longer defines a specific disease class within MDS, but rather is a qualifier suffix that is applied to any of the MDS entities described above. For example, a MDS case with multi-hit *TP53* mutations arising in a patient following chemotherapy for plasma cell myeloma should be diagnosed as "MDS with mutated *TP53*, therapy-related" and a MDS case with 6% BM blasts arising in a patient who received radiation for breast carcinoma should be diagnosed as "MDS-EB, therapy-related." Although it remains important to recognize therapy-relatedness of myeloid neoplasms, the first priority is to classify the disease according to its morphologic and genetic features [89]. As CCUS and CHIP can occur as a consequence of cytotoxic therapy and are precursor states to therapy-related MDS and AML [91], it is recommended to also qualify a diagnosis of CCUS and other pre-malignant clonal cytopenias as therapy-related if they follow cytotoxic therapy [92].

Any underlying germline predisposition mutation or syndrome should also be specified as a qualifier after the specific MDS entity. For example, a case with 12% blasts and germline *DDX41* mutation should be diagnosed as "MDS/AML, NOS, in the setting of germline *DDX41* mutation" and a case with multilineage dysplasia, < 5% blasts and

germline *RUNX1* mutation should be diagnosed as "MDS-NOS-MLD, in the setting of a germline *RUNX1* mutation." Care must be taken to diagnose MDS in patients with an underlying germline predisposition syndrome, since these conditions (particularly those associated with thrombocytopenia) may be associated with dysplasia at baseline. In such cases, the development of multilineage dysplasia, acquired cytogenetic or somatic molecular alterations, and/or progressive cytopenias indicate the emergence of MDS [93, 94].

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Declarations

Conflict of interest The authors declare no competing interests.

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