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Contemporary Approach to The Diagnosis and Classification of Myelodysplastic Neoplasms/Syndromes-Recommendations from The International Consortium for MDS (icMDS)

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Abstract

Myelodysplastic neoplasms/syndromes (MDS) are a heterogeneous group of biologically distinct entities characterized by variable degrees of ineffective hematopoiesis. Recently, two classification systems (the 5th edition of the WHO Classification and the International Consensus Classification) further sub-characterized MDS into morphologic and genetically defined groups. Accurate diagnosis and subclassification of MDS require a multistep systemic approach. The International Consortium for MDS (icMDS) summarizes a contemporary, practical, and multimodal approach to MDS diagnosis and classification.

INTRODUCTION

MDS originate from the expansion of a clonal hematopoietic stem/progenitor cell (HSPC) due to acquisition of recurrent genetic alterations, with varying degrees of morphologic dysplasia of hematopoietic cells, immunophenotypic aberrancies of blasts and maturing myeloid elements, and ineffective hematopoiesis resulting in peripheral blood cytopenias. MDS carries an inherent risk of transforming into acute myeloid leukemia (AML), with approximately 30% of cases eventually progressing to AML. (1) The MDS subclassification system put forth by the revised 4th edition World Health Organization Classification for Hematolymphoid Neoplasms (WHO-4R) relies mainly on the number of cytopenias at presentation, number of dysplastic lineages and the abundance of blasts in the bone marrow (BM) and peripheral blood (PB). Recent classification systems, including the 5th edition of the WHO Classification (WHO HAEM5)(2) and the International Consensus Classification (ICC)(3), share similar approaches to classifying MDS, including some entities defined by the presence of genetic alterations that supersede other categories, and other morphologically-defined entities (3, 4) (Table 1). Accurate diagnosis and subclassification of MDS requires the integration of clinical, morphologic, and genetic data, which, in turn, informs risk stratification and therapeutic management. (5) In this paper, we provide our multidisciplinary expert approach to applying these new classification systems

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for MDS and discuss their strengths and shortcomings using case examples, providing a practical approach to diagnosing MDS.

INITIAL EVALUATION AND DIAGNOSIS:

The diagnosis of MDS is a multi-step process that should incorporate clinical, histologic, immunophenotypic, and molecular findings. Patients with MDS may be clinically asymptomatic for years, with an incidental discovery of one or more cytopenias on routine laboratory analysis. Others may present progressive signs and symptoms related to sequelae of cytopenias, most commonly anemia, including fatigue, bleeding, or infections.

MDS is typically suspected by the presence of persistently unexplained cytopenias. WHO HAEM5 and ICC use the same thresholds for defining cytopenias (Hb <13 g/dL in men and <12 g/dL in women, absolute neutrophil count $<1.8 \times 10^9/L$, and platelets $<150 \times 10^9/L$) across clonal cytopenia of undetermined significance (CCUS), MDS, and myelodysplastic/myeloproliferative neoplasms (MDS/MPN). BM examination is conducted after excluding alternative causes of cytopenia. It requires a morphological evaluation and facilitates ancillary immunophenotypic and genomic characterization studies.

Morphologic evaluation of hematopoietic elements is critical in establishing a diagnosis of MDS and includes evaluation of blood and BM. Examination of PB is essential to confirm the presence of cytopenias, evaluate red blood cells (RBC), white blood cells (WBC), and platelet cytomorphologic features, and identify and quantify circulating blasts. Morphologic examination of the BM (aspirate and biopsy) is requisite in determining BM cellularity, assessing fibrosis and dysplasia, and enumerating blasts when present. The BM in MDS is typically hypercellular, but in a minority of cases, it may be normocellular or hypocellular (including a specific hypoplastic MDS subtype, recognized by WHO HAEM5 with BM cellularity < 30% in patients <70 years and < 20% in patients ≥ 70 years in the absence of increased blasts). (4, 6) The current recommendation for the threshold for dysplasia (Table 2) is $\geq 10\%$ in at least one hematopoietic cell lineage (erythroid, granulocytic, or megakaryocytic), which may not necessarily be the same as the cytopenic lineage. Dysplasia may be accompanied by increased myeloid blasts in the PB and/or BM, but the blast percentage in both PB and BM must remain <20%.

The genomic characterization of MDS has dramatically advanced during the past decade. Certain genetic alterations in MDS may be associated with specific morphologic manifestations (e.g., del 5q with small monolobated megakaryocytes and *SF3B1* mutation with ring sideroblasts) and clinical outcomes.

Cytogenetic abnormalities detected by conventional karyotyping and/or fluorescence in situ hybridization (FISH) most frequently are unbalanced, resulting in gains or losses of chromosomal material, and are found in about 50% of MDS cases. (7–9)

Incorporation of recurrent pathogenic mutations (present in >90% of MDS) via next-generation sequencing (NGS) is crucial in the diagnostic assessment of MDS, given their therapeutic and prognostic significance. (10) Over 30 driver mutations have been directly implicated in the pathogenesis of MDS (7) (Table 3), affecting RNA splicing,

DNA methylation, chromatin/histone modifications, and other pathways. The most frequent mutations involve RNA splicing and DNA methylation (11, 12)

Other gene mutations, such as *DDX41*, *RUNX1*, and *GATA2*, may represent germline alterations, predisposing individuals and potentially family members to myeloid neoplasms. Their detection at nearly heterozygous variant allelic frequency warrants further investigation to rule out germline origin. (7, 9, 13),(14) A comprehensive mutational analysis is essential in MDS as different genetic alterations correlate to other clinical features, risk categories, targeted therapies, and overall survival. (15)

Various methods are employed for the genetic characterization of MDS. (16, 17) Each method has strengths and limitations, necessitating a combination of these for a comprehensive understanding of genetic changes in MDS. These methods are summarized in Table 4. Comprehensive genetic analysis is crucial for the classification and risk stratification of MDS, which ultimately informs therapeutic decision-making and subsequent patient outcomes. (15)

Flow cytometry (FC) findings in MDS have been shown to correlate with cytomorphological and cytogenetic aberrations, as well as disease outcome (progression to AML and overall survival; OS). (18, 19) FC evaluation aids in diagnosing MDS with ambiguous morphology by identifying aberrant immunophenotypes, supporting a neoplastic origin of cytopenia. It quantifies blasts and immature myeloid cells, detects aberrant surface antigen expression, and identifies changes in intensity or pattern of antigens like CD13, CD33, CD34, CD45, and CD117 in mature myeloid cells. (20)

Several FC scoring systems have been published to assist MDS diagnosis (18, 21–24). The Ogata Score(25) utilizes four parameters, including the cluster size of myeloblast-related and B-progenitor-related cells, the CD45 ratio of lymphocytes to myeloblasts, and the side-scatter ratio of granulocytes to lymphocytes.

The International/European Leukemia Networking Group for Flow Cytometry in Myelodysplastic Syndromes (ELN-iMDS) recommends evaluating aberrancies in myeloid precursors, maturing granulocytic and monocytic components, and erythropoiesis using seventeen core markers.(26, 27) While flow cytometry is recognized as a helpful adjunct tool for diagnosing MDS, immunophenotypic abnormalities have not been formally incorporated into the diagnostic criteria for MDS by either the WHO (HAEM5) or the ICC.

When reporting the final diagnosis, it is recommended to state the overall diagnosis as “Myelodysplastic neoplasm/syndrome (MDS)” and provide the classification according to all three systems: (1.) the revised 4th edition WHO, (2.) HAEM5, and (3.) the ICC. Upon publication of the final 5th edition WHO Classification “Blue Book” monograph, the revised 4th edition WHO diagnosis could be omitted. While there is substantial overlap between the WHO 5th edition and ICC, a subset of cases will inevitably be classified differently when applying these systems, as described in detail in this article. The reason we are advocating for providing all three classifications at this time is to allow for a more inclusive approach with respect to clinical trial eligibility and treatment options and to

provide the treating physician with options to make the best management decision for the patient, on a case-by-case basis, when differences in terminology and classification exist. Providing this information will also allow for better documentation in the clinical records and research databases, which will hopefully facilitate future refinement and unification of these classification systems.

Clonal Hematopoiesis (CH)

WHO HAEM 5 and ICC formally acknowledge clonal hematopoiesis (CH) and related myeloid precursor lesions, marking the first inclusion of these concepts within their classification systems.

The spectrum of CH includes clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS). Idiopathic cytopenia of unknown significance (ICUS), representing unexplained cytopenia in the absence of documented clonality, is also included for the sake of completeness; however, ICUS is distinguished by its lack of evidence of clonality. The proposed minimum mutation variant allelic frequency (VAF) cut-off for CHIP and related disorders is $\geq 2\%$, mainly reflecting the lower limit of detection of historic NGS platforms.

Distinguishing CCUS from MDS requires a thorough morphologic evaluation of BM with distinction resting on the presence of morphologic dysplasia for MDS. Nevertheless, it must be recognized that many cases of CCUS overlap significantly with low-risk MDS with respect to their genetic landscape and outcome, and some eventually do evolve into *bona fide* MDS.(28)

Although the rate at which CH progresses to hematologic neoplasms is 0.5%-1% per year, recent data emphasize the need for risk stratification. Weeks et al. introduced an algorithm called “the clonal hematopoiesis risk score (CHRS),” which categorizes patients into three risk groups based on prognostic variables. (29) (Table 5). The 10-year risk of developing a hematologic neoplasm is $<1\%$ for the low-risk category. In contrast, the 10-year progression rates in the intermediate and high-risk categories are 8% and 52%, respectively. (29) The CHRS calculator is available at <http://www.chrsapp.com/>.

MDS with Defined Genetic Abnormalities:

Both the WHO HAEM5 and ICC subclassify MDS based on two broad categories either defined by genetic abnormalities and/or morphology. The presence of specifically defined genetic alterations generally supersedes the morphologic categories (in the absence of increased blasts) in both schemes.

MDS with low blasts and isolated 5q deletion (WHO 5th HAEM5) / MDS with deletion(5q) (ICC) (MDS-5q): Deletion of 5q is the most frequent chromosomal abnormality in MDS (15%). MDS-5q typically exhibits thrombocytosis or maintained platelet count with anemia and erythroid hypoplasia. One additional chromosomal alteration is permitted, excluding monosomy 7 or del(7q) (Table 1). Megakaryocytes are small and monolobated, sometimes forming clusters. (Figure 1). Ring sideroblasts and *SF3B1* mutation are common (~20%), and their presence does not exclude MDS-5q. (5) Patient

with MDS-5q have a favorable prognosis, with a median OS of 58 months and a relatively low risk of progression to AML. (5) Deletion 5q is considered a helpful predictive marker of response to lenalidomide in patients with MDS. Erythroid-stimulating agents (ESAs) are considered first-line therapy options for MDS-5q with symptomatic anemia. However, for patients with excessive erythropoietin (EPO) levels and a lack of response to ESAs, lenalidomide is the treatment of choice, and it results in improved responses in ~70% of patients.

MDS with low blasts and *SF3B1* mutation (WHO HAEM5) / MDS with mutated *SF3B1* (ICC) (MDS-*SF3B1*): MDS-*SF3B1* is characterized by the presence of an *SF3B1* mutation and is usually associated with macrocytic anemia. *SF3B1* mutations occur in 25% of all MDS but are present in about 80% of MDS with ring sideroblasts (RS). (30) Only WHO HAEM5 recognizes MDS with $\geq 15\%$ RS as a distinct morphologically defined category if *SF3B1* status is unknown or wild type but recommends using the terminology MDS with ring sideroblasts (MDS-RS). ICC classifies *SF3B1*-unmutated MDS-RS cases as MDS, NOS, irrespective of the number of RS. Both WHO HAEM5 and ICC require a minimum *SF3B1* VAF (5% and 10% respectively). MDS with RS and wild-type *SF3B1* usually have mutations in other genes that control RNA splicing, such as *SRSF2*, and have an inferior prognosis compared with MDS-*SF3B1*.

The presence of an *SF3B1* mutation correlates with distinct morphology, co-mutation patterns, gene expression profiles, and a favorable prognosis. (30) *SF3B1* mutations also occur in other myeloid and non-myeloid neoplasms (i.e. CLL) and in individuals with CHIP. However, in a patient with unexplained cytopenia, the ICC considers an *SF3B1* mutation (VAF $\geq 10\%$) to be MDS-defining, even in the absence of dysplasia or RS.

MDS-*SF3B1* has a relatively homogeneous disease phenotype and distinctive demographic features. The BM typically shows erythroid predominance with dyserythropoiesis featuring megaloblastoid features, binucleation and/or nuclear segmentation. Iron-stained aspirate smears typically show increased ring sideroblasts, which are defined as having ≥ 5 iron granules encircling one-third or more of the nucleus (Figure 2). Patients with MDS-*SF3B1* generally have higher neutrophil and platelet counts, lower BM blasts, and reduced risk of progression to AML compared to other MDS subtypes, and this may predict response to erythroid maturation agents such as luspatercept. (31)

MDS with biallelic *TP53* inactivation (WHO HAEM5) / MDS with mutated *TP53* (ICC)(MDS-*TP53*): MDS with biallelic/multi-hit *TP53* mutation (MDS-*TP53*) recognizes the unique biologic and clinical features in such cases, with high-risk features and complex cytogenetics. It is defined by cytopenia, dysplasia, and less than 20% blasts ($<10\%$ for ICC) and does not have features of pure/acute erythroid leukemia (Figure 3). A complex karyotype in the absence of *TP53* mutation does not qualify for this category, as these cases have less of an adverse prognosis. Bi-allelic loss of *TP53*, confirmed definitively through single-cell sequencing, is not routine in clinical labs. Instead, bi-allelic/multi-hit *TP53* alterations can be inferred based on specific scenarios: 1) >1 *TP53* mutation (assumed to be in trans, meaning the mutation affects two different alleles), 2) One *TP53* mutation associated with a deletion of 17p13.1 (*TP53* locus) or 3) One *TP53* mutation associated with

copy-neutral loss of heterozygosity (cn-LOH) at the 17p locus (Figure 4). The ICC requires a minimum *TP53* mutation VAF of 10% to qualify for MDS-*TP53*. In the absence of LOH information, the presence of a single *TP53* mutation with a complex karyotype (ICC) or a VAF $\geq 50\%$ (both ICC and WHO HAEM5) infers cnLOH.(32, 33) Monoallelic *TP53* mutated MDS cases are excluded from this category due to their less adverse prognosis compared to bi-allelic loss of *TP53* (34) and distinct biologic behavior, with the exception that for cases with 10–19% blasts, a single *TP53* mutation (with VAF $\geq 10\%$) suffices for the category of MDS/AML with mutated *TP53* (MDS/AML-*TP53*) by ICC criteria.

In the absence of readily available sequencing technologies, p53 immunohistochemistry (IHC) may be used as a surrogate for *TP53* status. (35) Aberrant overexpression (typically associated with missense and splice site mutations (35, 36)) or complete absence of staining (null pattern; associated with nonsense and early truncating mutations (frameshift)) are two well-recognized abnormal patterns of IHC that accurately predict the presence of *TP53* mutation. Here it is essential to recognize that when interpreting the stain, only 3+ nuclear staining should be regarded as aberrant overexpression (Figure 5). Unlike AML cases, where null patterns are more readily apparent, overexpression is more reliable for predicting mutations in MDS. The p53 immunohistochemical stain is agnostic to allelic state/copy number status, necessitating confirmation of *TP53* allelic state through genetic methods. MDS-*TP53* is a high-risk disease(37), which often rapidly transforms to AML(38), shows resistance to conventional therapies(9, 39), and dismal outcome (2-year overall survival, 12.8%).

Morphology Defined MDS

The morphologically defined categories of MDS in ICC and WHO HAEM5 are MDS with low blasts (MDS-LB; WHO HAEM5), / MDS-not otherwise specified (MDS-NOS; ICC), MDS with increased blasts (MDS-IB; WHO HAEM5) and MDS with excess blasts (MDS-EB; ICC). Two additional subtypes, hypoplastic MDS and MDS with fibrosis are recognized by WHO HAEM5 only (Table 1). These diagnoses are based on morphologic findings generally in the absence of the defining cytogenetic or mutational entities (MDS-5q, MDS-*SF3B1*, or MDS-*TP53*) outlined above; however, MDS-IB/EB does include cases with isolated del(5q) and/or *SF3B1* mutation that are excluded from these genetically defined categories due to the presence of increased blasts. The presence of increased blasts supersedes both del(5q) and *SF3B1* mutations because the favorable prognosis associated with these two genetic categories has been shown to be limited to cases with low blasts, and the presence of increased blasts is associated with increased risk of AML transformation is and reduced overall survival.

For morphologically defined MDS without increased blasts (**MDS-LB/NOS**), WHO HAEM5 has opted for optional inclusion of uni- versus multilineage dysplasia in subclassification of MDS, whereas ICC recommends subclassification based on unilineage versus multilineage dysplasia. Of note, retrospective analysis of large MDS cohorts has shown that the presence of multilineage dysplasia is associated with inferior outcomes in morphologically defined cases of MDS(40). Conversely, WHO HAEM5, recommends

specifying **MDS-LB with ring sideroblasts** for cases with $\geq 15\%$ RS that fail to meet criteria for MDS-*SF3B1*, usually due to wild-type or unknown *SF3B1* mutation status.

MDS, hypoplastic (MDS-h) is recognized as a distinct category by WHO HAEM5. It shows significantly decreased BM cellularity ($<30\%$ in patients <70 years and $<20\%$ in patients ≥ 70 years) and no increase in blasts in blood or BM. Patients are usually younger and tend to have more profound cytopenias at the time of diagnosis, with lower median white blood cells and absolute neutropenia. (4, 41)

MDS-h has clinical and pathologic overlap with aplastic anemia (AA) and paroxysmal nocturnal hemoglobinuria (PNH) disease spectrums. (6) The hypocellularity of BM aspirates in MDS-h may compromise morphologic, FC, and karyotypic analyses, causing difficulties in distinguishing MDS-h from other BM failure syndromes such as AA or inherited BM failure disorders. Detailed clinical information, including family history, is quintessential to qualify such cases accordingly, as has been shown in a recent historical review(42). An important clue favoring h-MDS is the presence of megakaryocytic dysplasia and micro-clustering of megakaryocytes in MDS-h, which can be highlighted using CD61 IHC. Hypocellular BM is sometimes a feature of some germline predispositions to myeloid neoplasia and germline assessment is recommended in patients who present with hypoplastic BM and cytopenias, in the absence of these germline mutations and outside of the context of germline predisposition to myeloid neoplasms, h-MDS lacks any specific cytogenetic or molecular abnormalities (e.g. somatic *PIGA* mutation, *GATA2*, *DDX41*). Cases with such mutations can have hypoplastic BM but should be classified as PNH in the absence of Bona fide features of MDS(43, 44).

MDS-IB/EB is subcategorized based on blast percentages in WHO HAEM5 (MDS-IB1 and MDS-IB2), and in the ICC, cases with 10–19% blasts (most of which overlap with MDS-IB2) are classified as **MDS/AML**. (Table 1). The ICC has created this novel category of MDS/AML to acknowledge the biologic continuum between MDS and AML in adult patients in order to broaden the eligibility of these patients for both MDS and AML-type therapies and trials at the discretion of the treating physician. While the WHO HAEM5 does not formally recognize an MDS/AML category, they also acknowledge this biological overlap and suggest that MDS-IB may be regarded as AML for clinical trial eligibility and treatment selection purposes. Around 15% of MDS cases show increased reticulin fibrosis ($\geq$ grade 2), which imparts an inferior prognosis across all MDS subtypes(45). WHO HAEM5 recognizes a subcategory of MDS-IB with fibrosis (**MDS-f**) defined as having grade 2 or 3 reticulin fibrosis in the setting of increased blasts (Figure 6). The core biopsy usually shows hypercellular BM with increased dysplastic megakaryocytes, including small forms and micromegakaryocytes. Notably, MDS-f cases are enriched for *TP53* mutations but the presence of bi-allelic *TP53* inactivation (multi-hit *TP53* status) supersedes MDS-f. (46) Given its prognostic relevance, we recommend performing a reticulin stain on all newly-diagnosed cases of MDS.

MDS in children (age <18 years) is managed distinctly and classified separately from adult MDS in WHO HAEM5 and the ICC and is not discussed in this review.

MDS Imitators

Morphologic dysplasia and cytopenias, while characteristic of MDS, are not exclusive to it and can stem from non-neoplastic conditions or germline disorders. A comprehensive evaluation for MDS necessitates identifying morphologic mimics (Table 6). (47, 48)

Nutritional deficiencies and exposure to toxins must be excluded when evaluating a patient for MDS as they are reversible causes of morphologic dysplasia and cytopenia. Cobalamin (vitamin B12) and folate deficiency can lead to pancytopenia, megaloblastoid morphology, and often dysplastic changes in the erythroid lineage. Copper and selenium deficiency and zinc toxicity(49, 50) can cause pancytopenia and dysplastic BM morphology (RS and erythroid and granulocytic vacuolization), mimicking MDS(51) (Figure 7). Various toxins can cause cytopenias and dysplastic changes that can be mistaken for MDS. Infectious etiologies should also be ruled out (i.e., hepatitis, tuberculosis, Coronavirus disease (COVID), and rheumatological conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), among others) as they can cause cytopenias and or overlapping features with MDS.

Arsenic trioxide, used in acute promyelocytic leukemia treatment, induces dysplasia in BM, resembling erythroid dysplasia in MDS. Tacrolimus, an immunosuppressive agent, can cause neutrophil bilobation, mimicking pseudo-Pelger-Huet change. Chronic alcohol use can lead to macrocytic anemia and dysplastic changes in the erythroid lineage, including vacuolization of pronormoblasts. Patients being treated with colony-stimulating agents (i.e., GCSF, GMCSF, and ESA therapies) can cause dysplasia, so biopsies are also recommended to be distant from clinical exposure to these agents.

Germline disorders and bone marrow failure syndromes like Fanconi anemia (FA), congenital dyserythropoietic anemia (CDA), and other congenital syndromes can initially present in adulthood and may show bone marrow morphologic findings that may overlap with or raise concern for MDS. (52) Some inherited bone marrow failure syndromes are associated with increased risk for MDS in childhood and early adulthood. (53) Although MDS is a somatically acquired disease that is not inherited, some genetic predisposition syndromes can increase the risk of developing MDS. These syndromes may be associated with pancytopenia, red cell aplasia, thrombocytopenia, and neutropenia and can even simulate MDS by demonstrating some dysplastic morphology. For example, germline *RUNX1* mutation can cause familial platelet disorders, which can present with thrombocytopenia and dysmegakaryopoiesis mimicking MDS. (54) Similarly, patients with heterozygous gain-of-function missense mutations in *SAMD9* or *SAMD9L* present with bone marrow failure, associated cytopenias, and a high risk of developing MDS with monosomy 7/del7q, at a young age. (55–58) Patients with telomere biology disorders (TBD) have an increased risk of developing clonal hematopoiesis and myeloid neoplasms. MDS in TBD patients has unique features, such as a higher frequency of hypo- or normocellular bone marrow and an increased frequency of ring sideroblasts. An abnormal karyotype is nearly universal in the setting of TBD-associated MDS, with monosomy 7 being the most common alteration. While a universal recommendation for surveillance in TBD patients does not exist, experts recommend following blood counts every 3–6 months and conducting annual bone marrow examinations.

Baseline dysplasia associated with some MDS predisposition disorders must not be confused with frank MDS. Establishing a diagnosis of MDS in the setting of germline predisposition syndromes typically requires a demonstration of clonal evolution (acquisition of additional somatic alterations or cytogenetic aberrations) and/or worsening cytopenias(54) and may require expert hematopathology consultation to differentiate expected morphologic changes in each disorder from changes worrisome for progression to MDS. Integration of the clinical history, bone marrow findings, cytogenetic studies, and specialized laboratory and molecular genetic testing is essential for accurate diagnosis and subsequent disease monitoring in such cases. (59, 60)

Systemic autoimmune and/or inflammatory diseases have been linked to MDS (61). VEXAS syndrome (acronym for vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a monogenic disease that is frequently associated with MDS (or also can be seen with multiple myeloma). The syndrome is associated with somatic mutations affecting *UBA1*, an X-chromosome gene encoding ubiquitin-like modifier-activating enzyme 1, and as a result, demonstrates a substantial male predominance, although rare female cases have been reported. Hematologic manifestations of VEXAS syndrome, particularly its presentation with macrocytic anemia, overlap with MDS(62) so awareness of this condition and sequencing for *UBA1* mutations is instrumental in establishing a correct diagnosis if clinical (autoimmune and inflammatory manifestations) or morphologic (vacuolization of bone marrow hematopoietic cells) is suggestive of VEXAS (Figure 8). VEXAS-associated MDS is distinct from classical MDS in its presentation and clinical course. (63) Although sporadic, recent progression from VEXAS to AML has been reported. (64)

MDS Prognosis and Risk Stratification

Various factors affect patient outcomes in MDS, and the prognosis of patients with MDS can be predicted using several scoring systems. The revised International Prognostic Scoring System-Revised (IPSS-R) developed by the International Working Group for Prognosis in MDS (IWG-PM) has served as a global standard for patient risk stratification and therapy recommendations. (65) The IPSS-R relies on hematologic and cytogenetic features but does not account for the gene mutations that play a crucial role in disease pathogenesis and serve as valuable prognostic biomarkers, as shown in multiple studies. (66–68)

The International Prognostic Scoring System – Molecular (IPSS-M) represents an update to the IPSS-R incorporating additional clinical and laboratory variables to improve risk stratification and more accurately predict OS and the likelihood of AML. IPSS-M includes the mutation status of 31 genes in addition to the BM blasts percentage, hemoglobin level and platelet count, and cytogenetic abnormalities. The IPSS-M is a six-tier risk stratification system, and provides a precise numerical risk score for each patient.

Among the various gene mutations incorporated into the IPSS-M, mutations in *TP53* (multi-hit), *FLT3*, and *KMT2A*-partial tandem duplication are the top genetic predictors of adverse outcomes. Conversely, *SF3B1* mutations are associated with favorable outcomes. It is important to note that the IPSS-M is a risk stratification tool, rather than a diagnostic tool and cannot be used to diagnose or classify MDS. Notably, the classification of MDS into molecular subgroups requires the determination of single gene mutation(s) as well as

co-mutation patterns and their association with clinical phenotypes and disease courses. While not currently taken into account in a systematic manner, future classification and risk stratification models will likely incorporate variant allelic frequency of the various mutations into these models as well. Compared with the IPSS-R, the IPSS-M has improved prognostic discrimination across all clinical endpoints; importantly, almost half of MDS patients are re-assigned to a different risk group when classified by IPSS-M rather than IPSS-R. The IPSS-M is applicable to de novo and secondary/therapy-related MDS. (5) The IPSS-M web calculator can be accessed at <https://mds-risk-model.com/>. Since the IPSS-M utilizes clinical, cytogenetics, and molecular data to assess the risk, it is suggested that all the available prognostic variables be incorporated in the final pathology report.

On behalf of the icMDS group, we provide a comprehensive and practical approach to MDS diagnosis and classification to facilitate accurate diagnosis, effectively guide treatment options based on disease-related risk, and foster clinical trial eligibility for patients with myelodysplastic neoplasms/syndromes.

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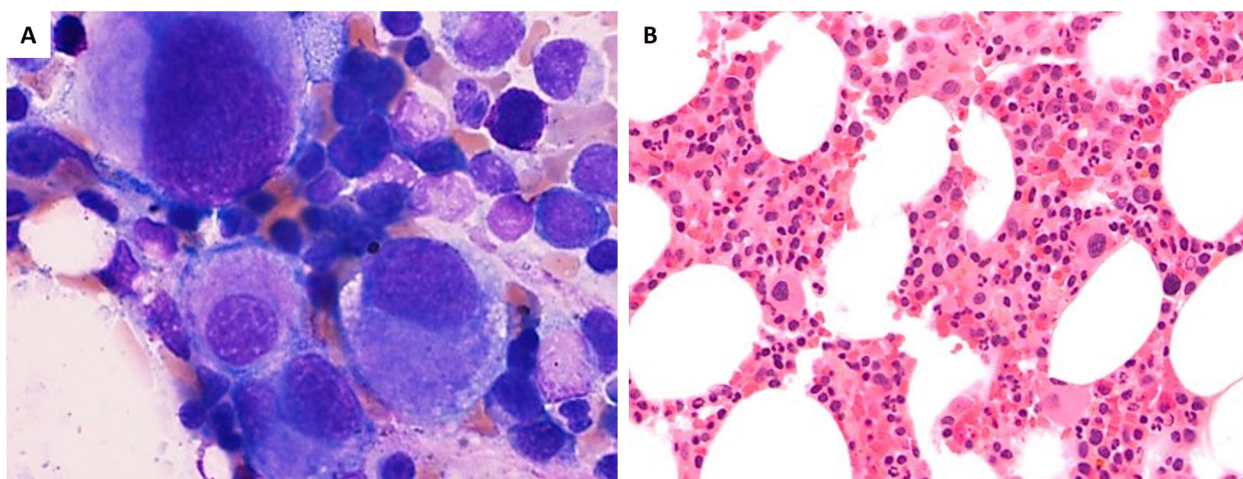


Figure 1. MDS-5q (A) The bone marrow aspirate smear shows increased megakaryocytes with characteristic small size and round, non-lobated nuclei (Giemsa, 1000x). (B) The bone marrow biopsy shows small non-lobated megakaryocytes (Hematoxylin and eosin, 200x).

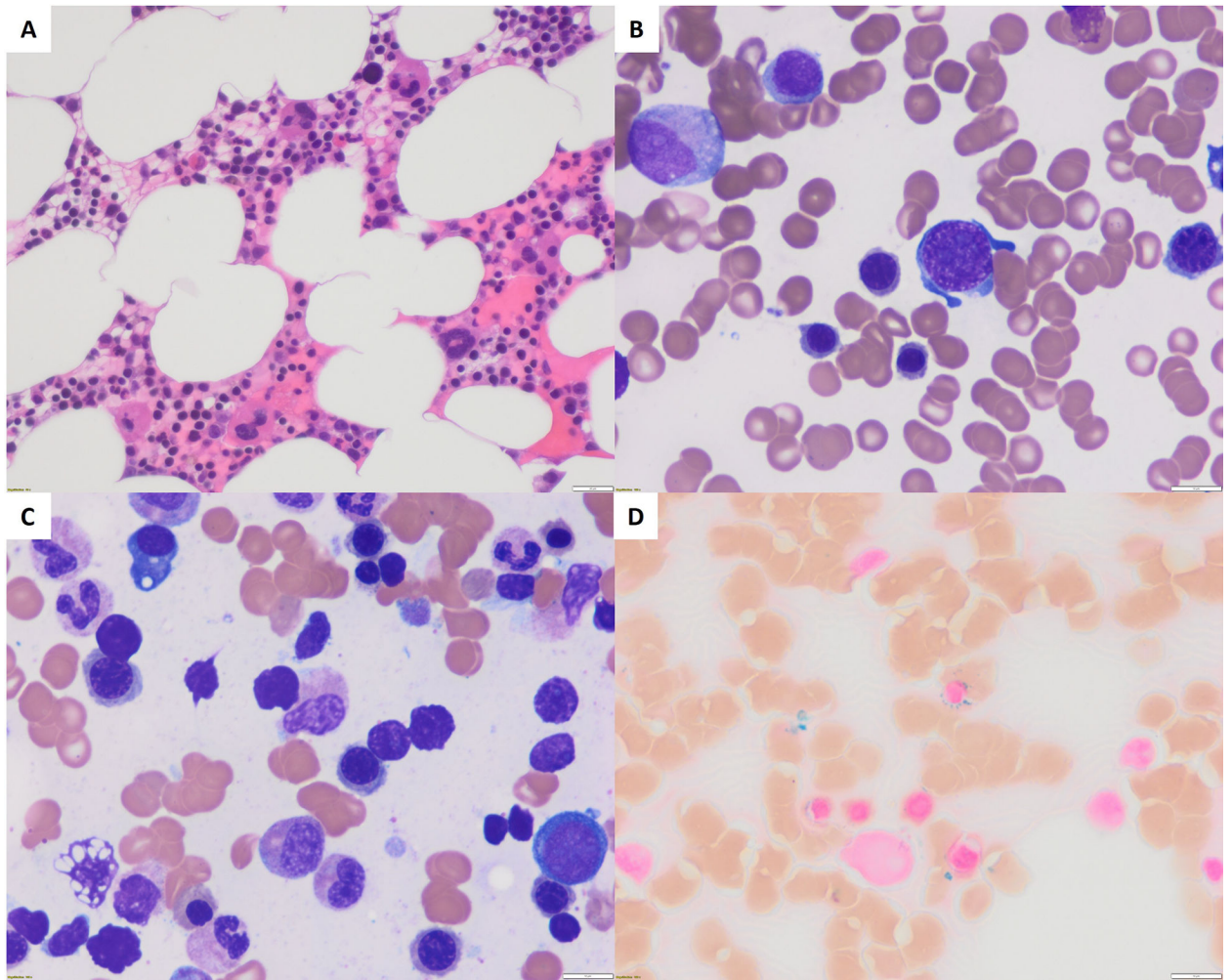


Figure 2.

MDS with *SF3B1* mutation- (A) The bone marrow biopsy shows relative erythroid predominance and small, dysplastic megakaryocytes (Hematoxylin and eosin, 200x). (B, C) the bone marrow aspirate smear shows increased erythroid precursors with megaloblastoid and dysplastic morphology (Giemsa, 1000x). (D) An iron-stained bone marrow aspirate smear shows increased ring sideroblasts (1000x).

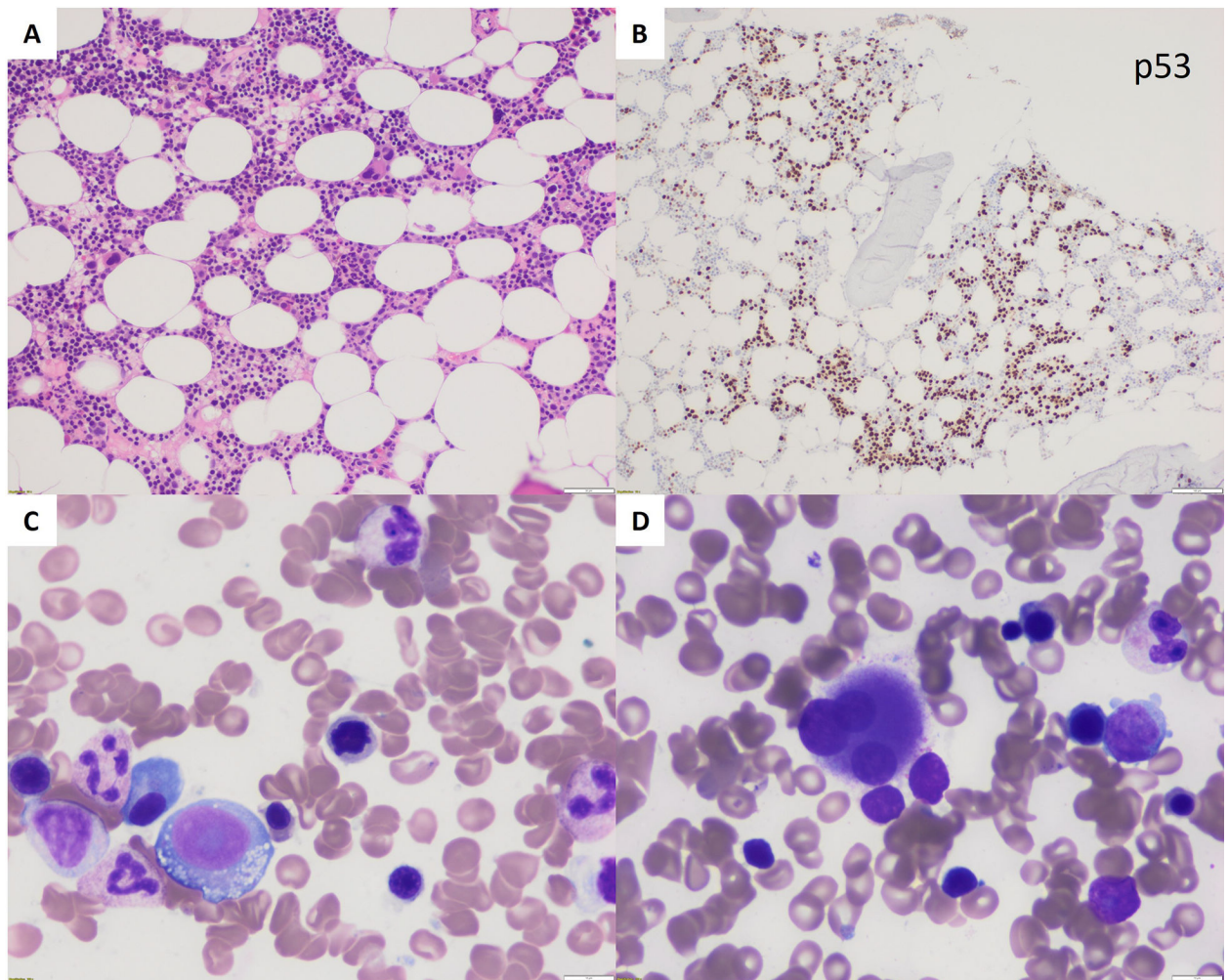


Figure 3.

MDS with biallelic *TP53* inactivation (WHO HAEM5) / mutated *TP53* (ICC) (A) The bone marrow biopsy is hypercellular and shows dysplastic megakaryopoiesis. (B) There is aberrant overexpression of p53 as indicated by numerous cells showing strong (3+) nuclear staining. (C, D) The bone marrow aspirate smear shows multilineage dysplasia. This case had a complex karyotype with two distinct *TP53* mutations (p.A161D and p.G279E).

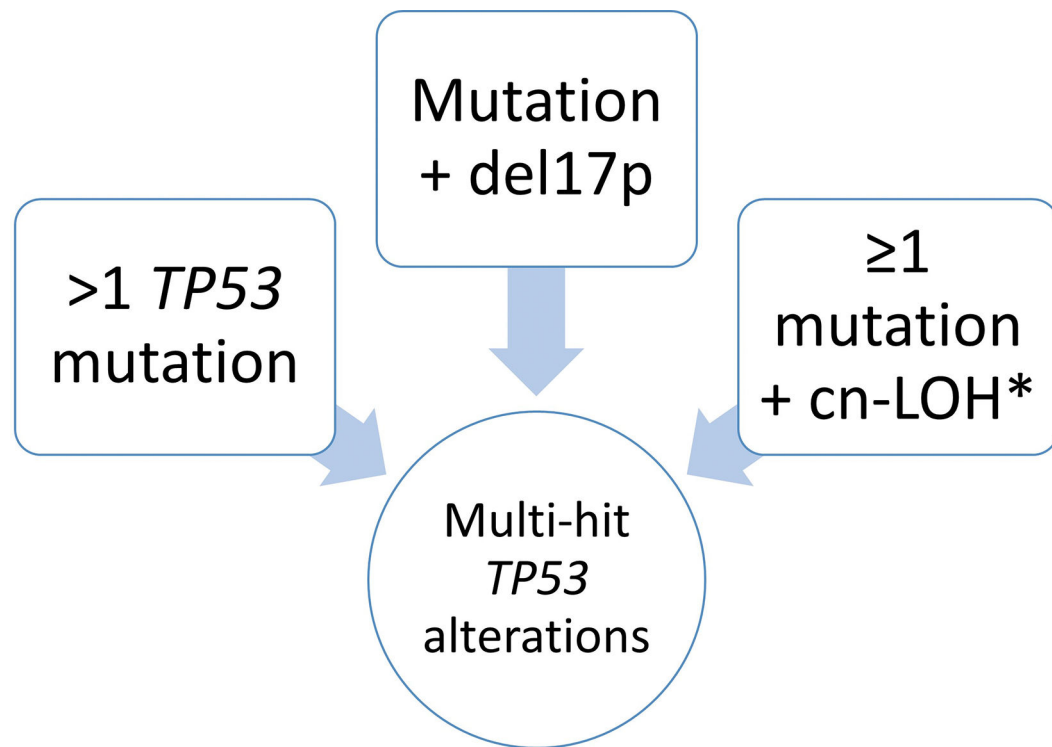


Figure 4.

Schematic representation of multi-hit *TP53* defining alterations. The presence of more than one mutation, mutation plus deletion of the wild-type allele, or mutation together with copy-neutral loss of heterozygosity is consistent with biallelic loss of *TP53*. cn-LOH may be implied by a *TP53* mutation variant allelic frequency of ≥50% if the allelic status of the wild-type *TP53* gene is unknown. *Mutation VAF>50% is a surrogate for cn-LOH in cases where cn-LOH cannot be determined, and a complex karyotype is also considered as presumptive evidence of LOH in ICC

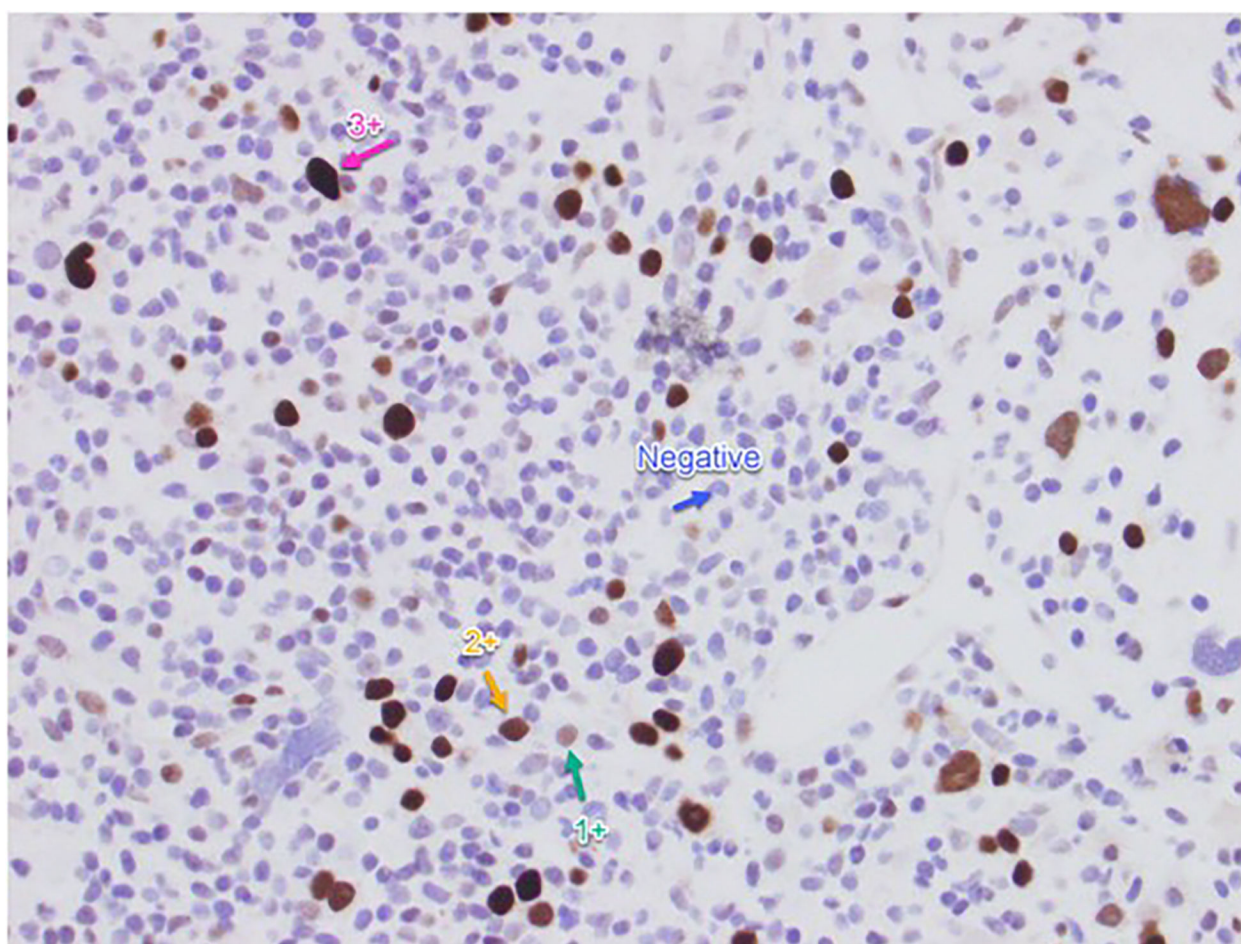


Figure 5. p53 IHC interpretation guide. Either aberrant overexpression (3+) or complete absence of staining (null pattern) is considered abnormal patterns of staining. When interpreting the IHC stain, only 3+ staining nuclei should be accounted for. Variable 1+ and 2+ staining may be seen in *TP53* wild-type cases and should not be interpreted as a mutant pattern.

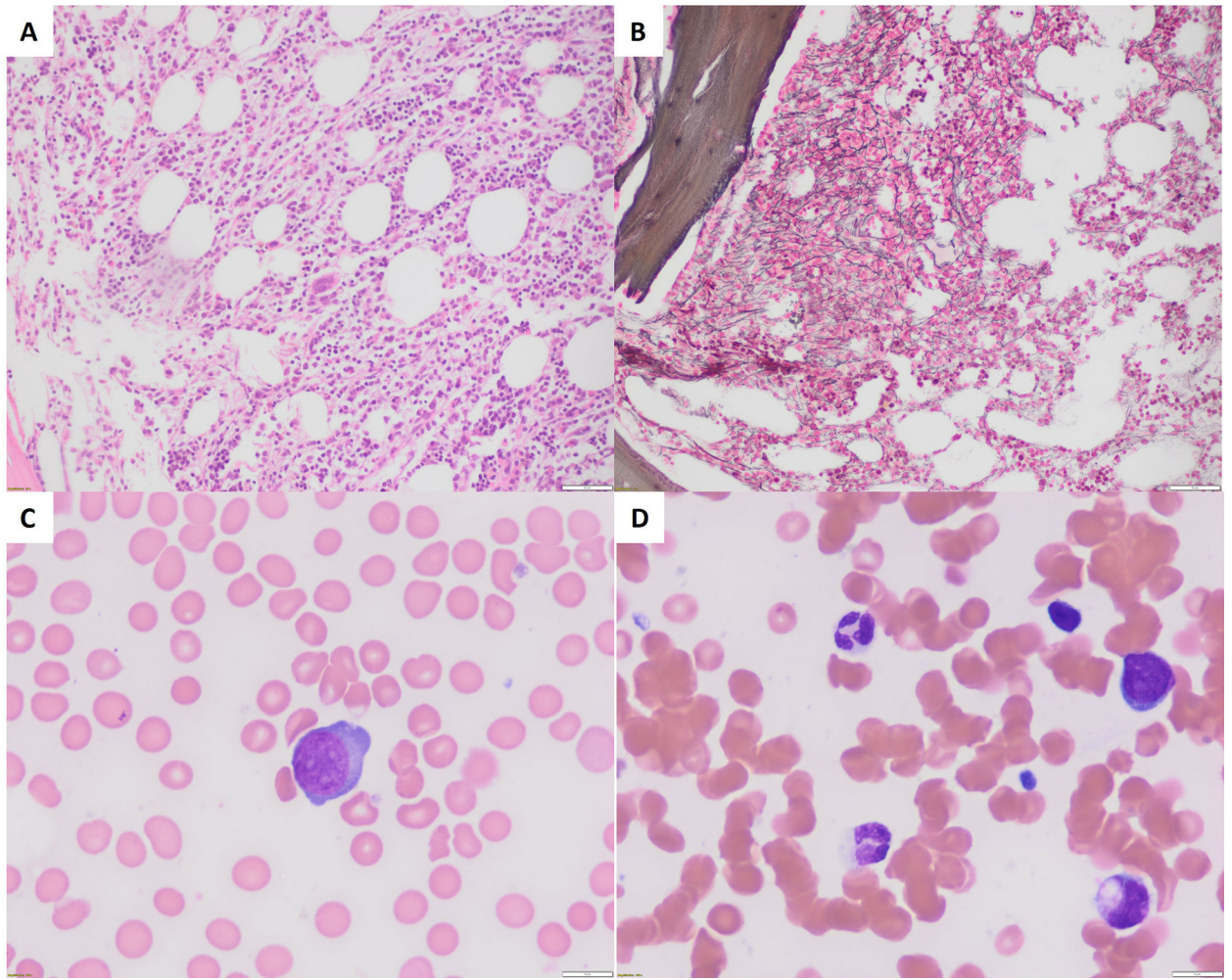


Figure 6. MDS with fibrosis (MDS-f) (A)The bone marrow is hypercellular with (B) increased ($\geq$ grade2) reticulin fibrosis. (C) Peripheral smear shows circulating blasts and (D) dysplasia is seen on bone marrow aspirate smear.

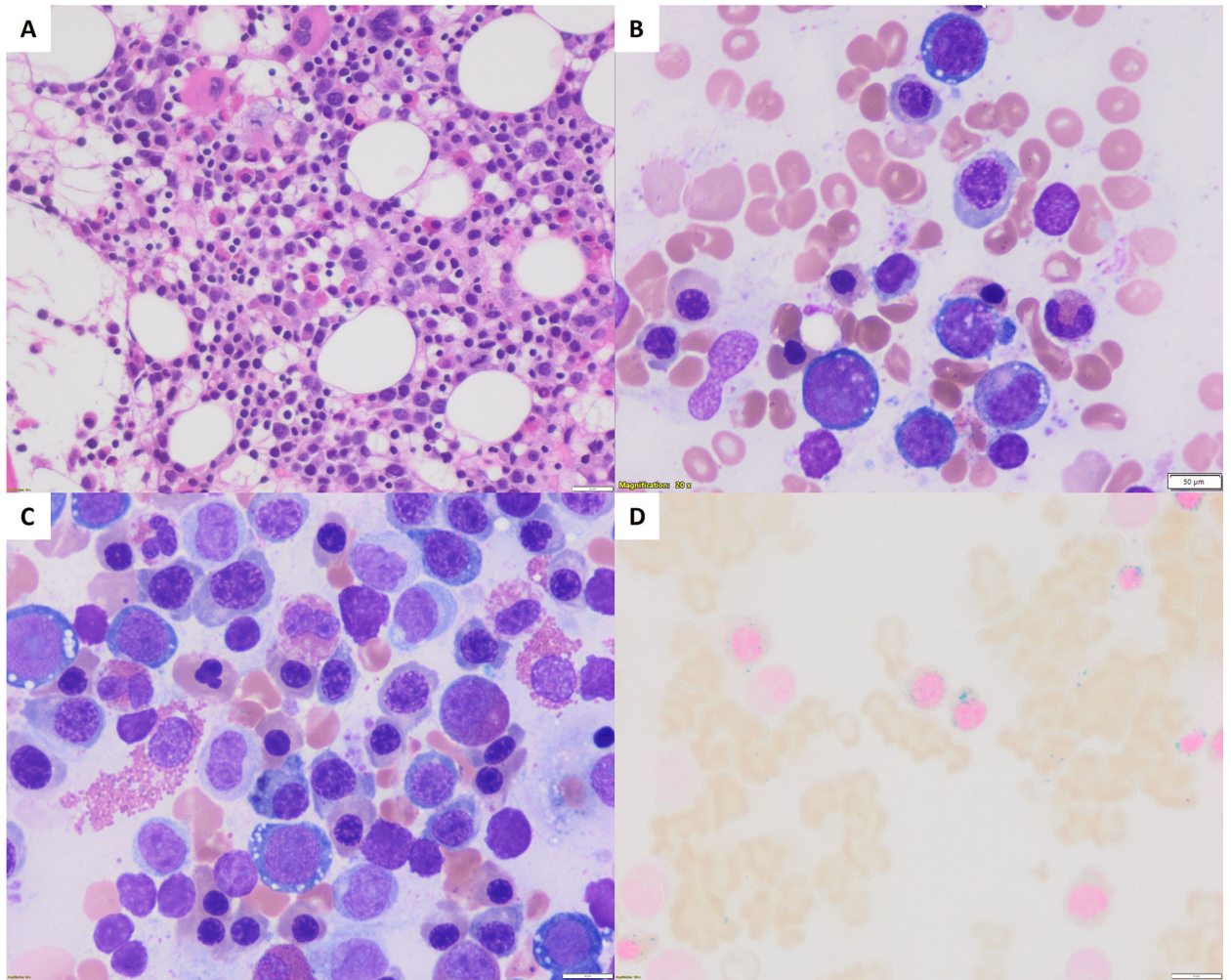


Figure 7. Copper deficiency (A) bone marrow biopsy shows hypercellular marrow with decreased granulocytic precursors. (B-C) The bone marrow aspirate shows frequent erythroid dysplasia, including cytoplasmic vacuolization. (D) An iron stain shows increased ring sideroblasts are increased, mimicking MDS.

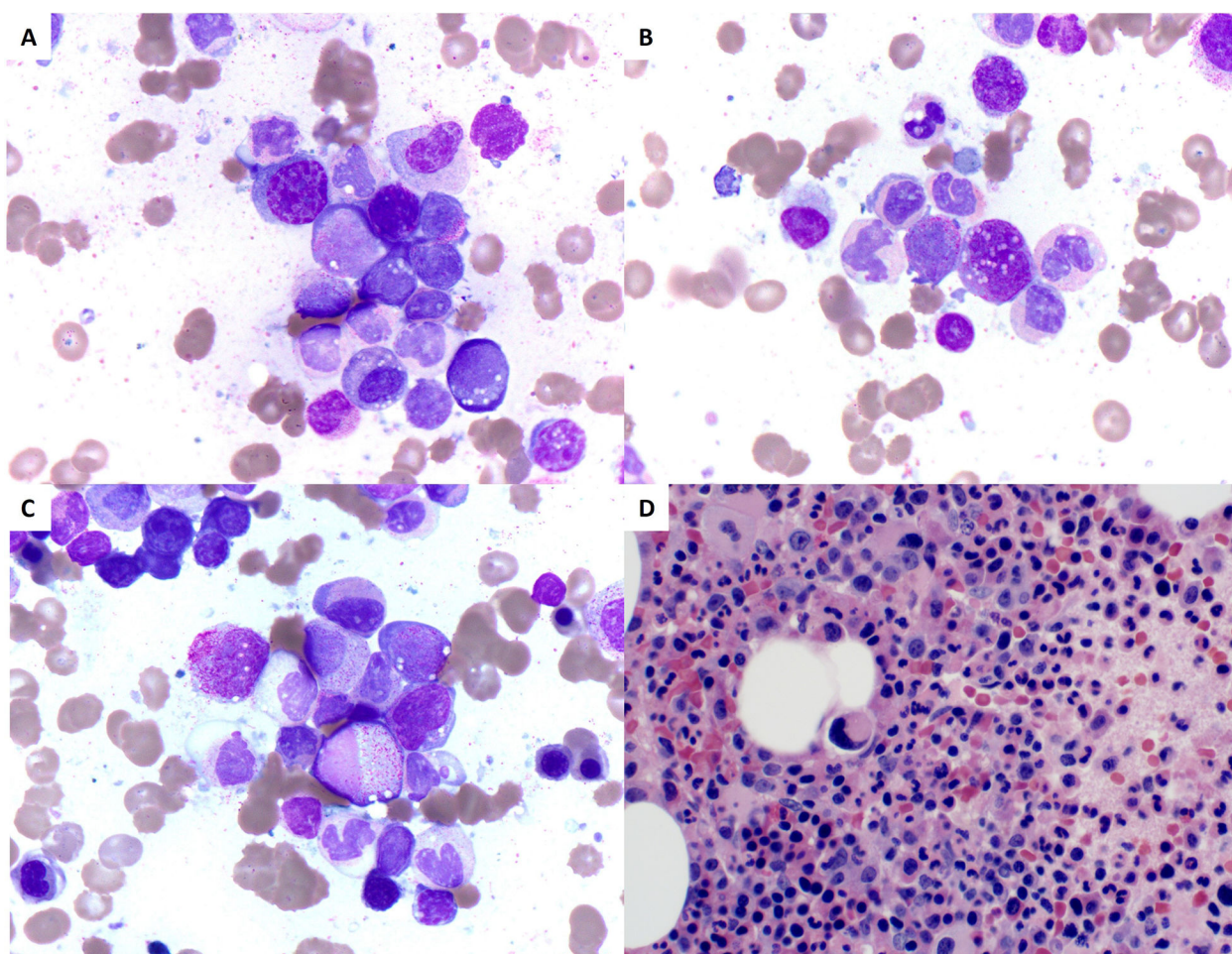


Figure 8. VEXAS syndrome: (A-C) The bone marrow aspirate shows myeloid and erythroid cells with cytoplasmic vacuolization and morphologic dysplasia. (D) The bone marrow biopsy is hypercellular and shows dysmegakaryopoiesis.

Table 1.
Myelodysplastic neoplasm/syndrome classification (WHO HAEM5 and ICC)

Myelodysplastic Neoplasm/Syndrome (MDS) Classification						
WHO HAEM5		ICC	MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion		MDS with del(5q) (MDS-5q)				
MDS with low blasts and <i>SF3B1</i> mutation ^a (MDS-SF3B1) or ≥15% ring sideroblasts		MDS with mutated <i>SF3B1</i> (MDS- <i>SF3B1</i>)				
MDS with biallelic TP53 inactivation (MDS-biTP53)		MDS with mutated <i>TP53</i> (MDS- <i>TP53</i>)				
		MDS without dysplasia				
MDS morphologically defined						
MDS with low blasts (MDS-LB)		MDS, NOS without dysplasia MDS, NOS with single lineage dysplasia MDS, NOS with multilineage dysplasia				
MDS, hypoplastic ^c (MDS-h)						
MDS with increased blasts (MDS-IB)		MDS with excess blasts (MDS-EB)				
MDS-IB1						
MDS-IB2		MDS/AML				
MDS with fibrosis (MDS-f)						
		MDS not otherwise specified (MDS-NOS)				

^a Detection of ≥15% ring sideroblasts may substitute for SF3B1 mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

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ICC VAF≥10%

BM cellularity of less than 30% in patients up to 70 years and less than 20% in patients 70 years old and older

* ICC *TP53* VAF≥10%; complex karyotype may substitute for *TP53* copy neutral loss of heterozygosity

**/† ICC guidelines (BM bone marrow, PB peripheral blood, *cnLOH* copy neutral loss of heterozygosity)

Table 2.

Morphologic manifestations of dysplasia in MDS

Dyserythropoiesis	Dysgranulopoiesis	Dysmegakaryopoiesis
Cytoplasmic Ring sideroblasts Vacuolization Periodic-acid-Schiff (PAS) positivity Nuclear Budding Internuclear bridging Multinuclearity Megaloblastic changes Karyorrhexis	Cytoplasmic Hypogranularity Pseudo-Chédiaq-Higashi granules Small size or unusually large size Auer rods Nuclear Hypo-segmentation (pseudo-Pelger-Huët) Hyper-segmentation	Cytoplasmic Micromegakaryocytes Nuclear Hypolobation Complete separation of nuclear lobes

Table 3.

Recurrent genetic alterations associated with MDS

Cytogenetic/chromosomal alterations	Somatic mutations and involved pathways
Unbalanced del(5q) Loss of chromosome 7 or del(7q) del(9q) del(11q) del(12p) Del(20q) Isochrome 17q Loss of chromosome 13 or del(13q)	RNA splicing <i>SF3B1, SRSF2, U2AF1, U2AF2, ZRSR2</i> DNA methylation <i>DNMT3A, TET2, IDH1, IDH2, WT1</i> Chromatin/Histone modification <i>EZH2, SUZ12, JARID2, ASXL1, KMT2, KDM6A, ARID2, ATRX</i> Transcription <i>RUNX1, ETV6, GATA2, IRF1, CEBPA, BCOR, NCOR2, CUX1</i>

Table 4.

Methods for establishing clonality in MDS

	G-banded karyotype	FISH	aCGH	NGS *	OGM	WGS
Genome Coverage	Whole	Targeted	Whole	Targeted	Whole	Whole
Ability to decipher individual clones	✓	✓	X	X	X	X
Ability to detect aneuploidy	✓	✓	✓	X	✓	✓
Copy Number variations (gain/ loss/ duplication, amp)	✓ ≥ 10Mbp	✓ targeted	✓	Selective panels	✓	✓
Structural abnormalities (translocation, inversion, insertion)	✓ ≥ 10Mbp	✓ targeted	X	X	✓	✓
SNV /LOH	X	X	X/ ✓	✓ targeted	X	✓
Sensitivity	1–3 metaphase	0.4~5%	~20%	1~10%	~20%	~20%

FISH: Fluorescence in situ hybridization; aCGH: Array comparative genomic hybridization; NGS: Next generation sequencing; OGM: Optical genomic mappings; WGS: Whole genomic sequencing; Mbp: Mega base pair; SNV: Single nucleotide variant; LOH: Loss of heterozygosity.

* NGS-based RNA sequencing may be used to detect gene fusions in cases of suspected NGS; the detection of AML-defining fusions will exclude the diagnosis of MDS, if appropriate AML criteria are met.

Table 5.

Clonal Hematopoiesis Risk Score (CHRS)

Prognostic Variable	0.5	1	1.5	2	2.5
Single DNMT3A	Present	Absent	-	-	-
High risk mutation	-	Absent	-	-	Present
Mutation number	-	1	-	≥2	-
Variant allele frequency	-	< 0.2	-	>2	-
Red cell distribution width	-	< 15	-	-	≥ 15
Mean Corpuscular volume	-	< 100	-	-	>100
Cytopenia	-	CHIP	CCUS	-	-
Age	-	< 65 years	> 65 years	-	-

Risk Assessment:

- Low risk: A score ≤ 9.5
- Intermediate risk: A score between 10 to 12
- High risk: A score of ≥ 12.5

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Table 6.

Secondary causes of dysplasia and cytopenias

Medications	
Isoniazid	
Cotrimoxazole	
Tacrolimus	
Mycophenolate	
Ganciclovir	
Chemotherapeutic agents	
G-CSF	
Nutritional/Toxic	
Excessive alcohol intake	
Vitamin B12/Folate deficiency	
Copper deficiency	
Heavy metal (arsenic, lead, or zinc) toxicity	
Hereditary	
Autosomal dominant Pelger-Huet (mutation in LBR gene)	
Congenital dyserythropoiesis	
Germline predispositions	
Infections	
HIV/AIDS	
Parvovirus B19	
Other hematopoietic stem cell disorders	
Fanconi anemia	
Aplastic anemia (AA)/Paroxysmal nocturnal hemoglobinuria (PNH)	
VEXAS syndrome	