

Classification of myelodysplastic syndromes

Identity

Note Basis of classification in conformity with WHO recommendations.

The classification of [acute myeloid leukemia](#) (AML) and myelodysplastic syndromes (MDS) includes clinical data (previous history, age) and biologic characteristics (morphology, cytochemistry, immunophenotype, cytogenetic and molecular biology). The separation of homogeneous classes allows us to distinguish prognostic parameters and to identify groups of patients sensitive to drugs or to specific treatment. Recurrent cytogenetic abnormalities are strong prognostic indicators in AML and MDS. Molecular studies of structural chromosomal changes have enabled the cloning of genes located at chromosomal breakpoints and have helped to characterize the proteins involved in leukemogenesis. Morphologic studies remain important because of a strong correlation with cytogenetic and molecular abnormalities.

Clinics and Pathology

Note The myelodysplastic syndromes (MDS) are clonal hematopoietic disorders characterized by cytopenia and bone marrow dysplasia. This is resulting from proliferation, differentiation and apoptotic processes of hematopoietic precursors with frequent evolution to acute myeloid leukemia (AML). Anemia, neutropenia or thrombocytopenia, separated or in combination, despite a hyper or normo-cellular bone marrow, define MDS. The concept of myelodysplastic syndromes has evolved gradually from the description of a group of anemias previously described as "refractory anemias".

MDS is a somewhat heterogeneous group of patients with regard to clinical presentation, laboratory findings and prognosis. Methods for evaluating the potential clinical outcome have been developed by taking into account the hematological presentation (degree of cytopenia, classification in subgroup based on the percentage of bone marrow blast cells), bone marrow karyotype and some clinical parameters, mainly age.

Primary and secondary MDS are defined by taking into account the prior patients history: previous treatments with chemotherapy, radiotherapy or professional exposure to toxic substances are defining secondary MDS (sMDS) or "primary" MDS. Cytogenetically, a difference between the two groups is the complexity of abnormal karyotypes since single chromosome aberrations are typical for primary MDS, while multiple

changes are more frequently seen in secondary disorders. Some drugs may have specific targets such as: hydroxurea for 17p, topoisomerases inhibitors for 11q23 and 21q22. The genetic changes in the malignant cells of MDS result mainly in the loss of genetic material, including probable tumor suppressor genes.

Primary MDS

MDS IN ELDERLY PATIENTS: MDS is primarily a disease of the elderly. The median age of patients varies from about 60 years to 75 years. Patients below the age of 50 years are less frequent and their number varies greatly among different series in the literature. MDS subtypes, as defined by the FAB-working group, have prognostic significance in the elderly, in whom survival and incidence of AML progression are more favorable in lower stages of the disease (lower blast cell count). MDS characteristically responds poorly to AML chemotherapy, with prolonged cytopenias and poor remission rates. Less than 50% of MDS cases have cytogenetic abnormalities at presentation; this frequency increases with progression and includes gain or loss of major segments of chromosomes ([-5/del\(5q\)](#), [-7/del\(7q\)](#), [+8](#), [+9](#), [+11](#), [del\(11q\)](#), [del\(12p\)](#), [del\(17p\)](#), [-18](#), [+19](#), [del\(20q\)](#), [+21](#)).

CHILDHOOD MDS: MDS appears to be uncommon in children but it is characterized by a higher rate of progression to overt acute leukemia. Their classification has been the subject of controversy. If some cases of [childhood MDS](#) are similar to adult MDS, others have a more "myeloproliferative" presentation with prominent hepato-splenomegaly, leucocytosis, monocytosis, frequent skin involvement, and presence of immature cells in the peripheral blood. These cases have been referred to chronic myelomonocytic leukemia (CMML) or juvenile chronic myelogenous leukemia ([JCML](#)). This feature is primarily observed in infancy and early childhood.

THE CRITERIA FOR DIAGNOSIS: The diagnosis of MDS is mainly morphological and based on the presence of dysplastic features in the peripheral blood and bone marrow. The French-American-British (FAB) Cooperative Group has proposed (1982) a classification based on easily obtainable laboratory information; despite its effectiveness for classifying MDS, omission of biological parameters such as marrow cytogenetics and the degree of cytopenia makes necessary a reappraisal of certain novel aspects of the diagnosis and prognosis.

Secondary MDS (sMDS)

Cases of MDS related to chemotherapy and radiotherapy (sMDS) are increasingly being recognized as long-term complications of cancer therapy. This entity is not clearly different from sAML (sAML frequently evolves from a preceding myelodysplastic phase. The bone marrow blast cell cut-off of 20% that distinguishes sAML from sMDS, often depends on the hematological follow-up of at-risk groups of patients who have received chemotherapy and/or radiotherapy. If early bone marrow examination is performed, MDS may be diagnosed but AML could be diagnosed too if bone marrow examination is delayed until the

blast cells appeared in the peripheral blood. sMDS/AML after chemotherapy is diagnosed after lymphoma therapy with a percentage of relative risk ranging from 2.2 to 3.3 at 15 years. For both sMDS and sAML the most frequently involved drugs include alkylating agents, epipodophyllotoxins and anthracyclins. The majority of sMDS/AML are morphologically characterized by multilineage myeloid dysplasia; the great majority have chromosome abnormalities, the most common being the loss of genetic material of either part or all of chromosome 7 and/or 5 (7q/-7, /5q-, -5). sMDS has a rapid course and a short survival.

Morphological classification

Historical background and basis for the practical classification

The diagnosis of MDS is often made unexpectedly after a routine blood count. There are no specific symptoms other than those related to progressive bone marrow failure.

PERIPHERAL BLOOD: Patients are commonly anemic with normal or low reticulocyte counts. Anemia is usually normocytic or macrocytic. In cases with severe dyserythropoiesis in the bone marrow, the peripheral blood may show poikilocytosis and anisocytosis. The neutrophil count is variable and may be low. Neutrophil granulations may be reduced or not visible on MGG stained smears. Thrombocytopenia is common in MDS but the platelet count may be normal.

BONE MARROW: In the bone marrow, different degrees of morphological and functional abnormalities of erythroid (DysE), megakaryocytic (DysM) and granulocytic (DysG) lineages are a hallmark of the disease. In the granulocytic lineage, hypogranular cells may be associated with other abnormalities such as persistent cytoplasmic basophilia and vacuolisation; abnormal nuclear features are common, such as hyposegmented forms (pseudo Pelegre-Huet) or binucleated cells. Abnormal eosinophils, basophils and mast cells are rarely seen. Cytochemical abnormalities include reduced myeloperoxidase or inappropriately increase in alpha-naphthyl esterase activity. Megakaryocytic dysplastic features are particularly frequent in MDS and include megakaryocyte hypoploidy (micromegakaryocytes) and multinucleated megakaryocytes or large monolobed cells.

WHO Reassessment of MDS morphological classification

The FAB cooperative group initially proposed (1982) morphological criteria to distinguish between MDS and AML on the basis of the arbitrary bone marrow blast count and divided MDS into five subtypes: Refractory anemia (RA), RA with excess of blasts (RAEB), RA with excess of blasts in Transformation (RAEBT), RA with ringed sideroblasts (RARS), Chronic myelomonocytic leukemia (CMML). This subdivision is mainly based on the percentage of blasts in the peripheral blood and bone marrow (RA to RAEBT) but, also, on the absolute peripheral blood monocyte count (CMML) and the percentage of ring sideroblasts (RARS).

Readjustment of this FAB classification has recently been undertaken in order to resolve some ambiguities (WHO Classification). RAEB T is suppressed as category and is included with AML M2.

Disease Refractory anemia (RA)

Clinics [Refractory anemia](#) demonstrates less than 5% bone marrow blast cells. RA should be included in a more general group of myelodysplastic syndromes without excess blasts. The typical presentation is anemia but the first hematological manifestation could be thrombocytopenia alone, or more rarely neutropenia alone (refractory cytopenia). Since refractory cytopenias (RC) are heterogeneous with regard to their morphology, clinical features and survival, it has been proposed to separate RC patients in two categories: RC with multilineage dysplasia (mRC), a distinct subset with an unfavorable clinical outcome and RC with minimal dysplasia (RC).

Disease Refractory anemia with excess of blasts (RAEB)

Clinics The [RAEB](#) category remain unchanged and as previously described include MDS patient having more than 5 and less than 20% bone marrow blasts. Suppressing the RAEB-T category. This subclass was identical to RAEB except for a higher percentage blasts: between 20 and 30% in the bone marrow and/or more than 5% in the peripheral blood. Most of these patients have been recognized to have an AML M2 outcome. For that reason, it has been suggested that patients with more than 20% of blast cells in the peripheral blood or bone marrow may be considered as acute myeloid leukemia M2. Presence of Auer rods that was an indication for RAEBT is no more taken into consideration for the classification. Splitting RAEB into two classes: RAEB I and RAEB II. It has been recommended to separate RAEB patients in two groups: RAEB I with < 10 % blasts in the bone marrow and/or 1 to 5% blast cells in the peripheral blood. RAEB II with 10-20 % in the bone marrow and/or 5% to 20% blast cells in the peripheral blood.

Disease Refractory anemia with ringed sideroblasts (RARS).

Clinics Restricting the definition of [RARS](#). Ineffective erythropoiesis, dysplastic erythroid precursors and progressive anemia characterize RARS. The FAB has defined RARS as <15% sideroblasts. Some confusion has arisen in using this point. It has been shown that patients with increased sideroblasts and other myelodysplastic features have a more severe course than those without additional dysplasia. The "pure" RARS (without dysplasia) is characterized by a very low risk of progression to leukemia and has usually a high percentage of bone marrow erythroblasts and ringed sideroblasts. An increase in ring sideroblasts in other MDS/MPS with dysplasia should be mentioned as an additional factor but is not crucial for classification.

Disease Chronic myelomonocytic leukemia (CMML)

Clinics The arbitrary definition of the FAB [CMML](#) subtype has led to some controversy. The minimal monocyte count for CMML was set at $1 \times 10^9/l$. Many subsequent studies have recognized the heterogeneity that exists within the subgroup of CMML. Some patients present with a

modest monocytosis and leukocytosis (MDS/CMML) and others have an extreme leukocytosis and extramedullary hematopoiesis characterized by splenomegaly, serous effusions or skin infiltration (MPS/CMML). Whether dysplastic and proliferative CMML represent different phases of a single disease or are distinct entities remains unclear. Disparate results have been obtained concerning median survival between these two subtypes. The WHO classification recommends putting CMML into a new category between Myelodysplastic and Myeloproliferative syndromes (MDS/MPS). The WHO classification recommends keeping only the CMML patients with myeloproliferative features defined as having $> 1 \times 10^9/l$ monocytes in the peripheral blood. The WHO classification recommend to classify CMML in a separate group (SMD/SMP) having both criteria of MDS and MPS.

Disease Atypical Chronic Myeloid Leukemia (a-CML)

Clinics This new definition,(SMD/SMP), simplifies the distinction between CMML and another MPS category, [atypical chronic myeloid leukemia](#) which may have an increased monocytic count in addition to significant increase in circulating immature granulocytes; a-CML is usually characterized by more obvious myelodysplastic changes. Whether CMML and a-CML are separate disorders or part of a spectrum of MPS with various dysplastic features remains unclear. The WHO classification recommend to classify a-CML into the SMD/SMP group. Amongst patients that are presenting as MDS or MPS (depending on their WBC count), a peculiar morphological syndrome is the " abnormal chromatin clumping syndrome" (ACCS). This subtype is only based on morphologic features and is characterized by abnormal chromatin clumping of the granulocytic lineage. No precise correlation has been yet demonstrated with chromosomal changes in the few cases described in the literature the clinical outcome is poor.

Disease "Unclassified" MDS

Clinics Other distinct MDS subgroups, such as hypocellular MDS and MDS with myelofibrosis have been recognized. Some cases of MDS with abnormal eosinophilia and MDS associated with abnormal mast cell have been described.

Genetics

Cytogenetic classification.

CHROMOSOMAL ABNORMALITIES IN PRIMARY MDS:

Myelodysplastic syndromes are typical cytogenetic models of the leukemogenesis process: the clonal population progresses through a chronic phase that can last for years, to frank leukemia. Chromosome abnormalities should be taken in consideration in addition to specific hematological abnormalities in order to define new MDS syndromes. Most investigators working on MDS integrate morphology and cvtogenetics in diaconis and classification. In (primary) MDS. non-

random chromosomal aberrations contribute to characterized distinct clinico-pathological entities in which cytogenetic findings correlate with morphological features or with the clinical course of the disease. In primary MDS, around 50% of karyotypes are abnormal, depending on the patient series and on the techniques used. Cytogenetic studies have focused on chromosomal deletions as the most typical changes in MDS. Molecular genetics allow narrowing of the loss of genomic regions and are useful to discover cryptic deletions. It is obvious that some cases of MDS will need multi-color FISH to identify complex chromosomal rearrangements.

PATTERNS OF CHROMOSOMAL ABNORMALITIES IN SECONDARY MDS (sMDS): The incidence of chromosomal abnormalities is higher in sMDS (more than 85%) than in the corresponding de novo diseases (about 50%). The ploidy is different in secondary MDS and primary MDS: hypoploidy is clearly more frequent in secondary MDS. Several numerical and/or structural chromosomal abnormalities are frequently associated with sMDS: among the most common, there is the association of abnormalities of chromosomes 5 and 7 (-5 or 5q- and -7 or 7q-).

KARYOTYPIC/MORPHOLOGIC CORRELATION IN MDS: Attempts to correlate cytogenetic changes with the morphological subtypes of MDS as defined by the initial FAB criteria have not been successful. However, some molecular changes and karyotypic aberrations are more or less correlated with a specific cytological presentation, mainly in primary MDS. The major chromosomal anomalies are the following: del(5)q, monosomy 7, del(20)(q), trisomy 8 and less frequently +6, +13, +21, t(5;12)(q33;p13), other 12p changes, t(3;5)(q25;q34), inv(3)(q21q26), rearrangements involving 1q, 11q23, 17p-/17 and X.

Cytogenetics

Cytogenetics **del(5q), the "5q- syndrome"**

Morphological An interstitial deletion of the long arm of chromosome 5, [del\(5q\)](#), has been identified as a non-random aberration in a specific group of refractory anemia (RA). This "5q-" syndrome is characterized by a distinct clinico-morphological presentation: high prevalence of elderly females with a relatively good prognosis. This syndrome is characterized by a macrocytic anemia, a normal or high platelet count, a modest leukopenia, no excess blasts in the bone marrow and, as hallmark of the disease, the presence of monomorphous large normoploid megakaryocytes with hypolobulated nuclei and without other megakaryocytic abnormalities. Karyotypic clonal evolution and transformation into acute leukemia are rare. Cytogenetically, the 5q- appears polymorphic since the breakpoints as well as the size of deletion are variable with a critical region of deletion between bands q31 and q33. This genomic region is extremely rich in genes encoding growth factors. del(5q) has also been observed in other MDS/AML. In secondary (sMDS/AML) cases, del(5q) is frequently associated with other chromosomal abnormalities, particularly chromosome 7. In that

case, the dysmegakaryopoiesis is more polymorphic with the association of monolobed megakaryocytes and other types (mainly micromegakaryocytes). When re-examined by FISH some cases of del(5q) are found to be more complex than expected (with cryptic t(5;7) for example). These abnormalities are often impossible to detect using conventional cytogenetics.

Monosomy 7

as well as partial deletion of the long arm of chromosome 7, [-7/del\(7q\)](#), is among the most typical changes of sMDS with loss of a narrow genomic segment at 7q22.1. Chromosome 7 deletions are associated with bad prognosis. Monosomy 7 in primary MDS is often found in children '[childhood monosomy 7](#)' with juvenile chronic myelomonocytic leukemia (JCML) and in [familial -7](#) MDS. [RAS](#) gene mutations or loss of the [NF1](#) gene are thought to be critical events in the pathogenesis of MDS with -7. Monosomy 7 and del(7q) are frequent in sMDS and quite rare in primary MDS; these deletions are variable in size and are always interstitial with two main zones at 7q22 and 7q32-34. Monosomy 7 is often associated with other chromosome changes. Chromosome 7 anomalies are more frequent in RAEB and CMML (20%) than in RA with abnormal karyotypes. Monosomy 7 is frequently associated with circulating and bone marrow micromegakaryocytes. In sMDS, 40 to 60% of cases have simultaneous del(7q) / -7 and del(5q) / -5. Patients with del(7q) and -7 have a severe outcome with sensitivity to infections and therapy resistance. Although non-specific, monosomy 7 is the most common cytogenetic abnormality in childhood MDS. MDS and AML in childhood may be associated with [Fanconi's anemia](#), Kostmann's syndrome, Schwachman-Diamond syndrome, Down's syndrome and other inherited diseases characterized by chromosome breakage.

del(20q)

A chromosome [20q deletion](#) is associated with about 5% of primary MDS. Erythrocytic and megakaryocytic lineages appear to be involved preferentially. The majority of cases have an interstitial deletion between 20q11.2 and q13.3. del(20q) can be associated with both all subtypes of MDS (AR to AREB and CMML) and myeloproliferative syndromes (MPS). del(20q) is frequently associated with del(7q) / -7 and/or 3 del(13q). As a single anomaly, the del(20)(q) has a favorable prognosis.

del(13q)

Loss of interstitial material of the long arm of chromosome 13, [del\(13q\)](#), may occur in different types of AL and MDS or more frequently in MPS. del(13q) can be an isolated anomaly or associated with other karyotypic aberrations. del(13q) is an interstitial deletion; q14 and q21 are consistently deleted and this region contains a number of candidate tumor suppresser genes. No precise morphological correlation has been identified to date.

del(11q)

Interstitial deletions of the long arm of chromosome 11, del(11q), with breakpoints at q14 and q23 are typically associated with MDS and bone marrow sideroblastosis.

Trisomy 8

[+8](#) is, like monosomy 7, one of the most frequent numerical aberration in MDS. Its prognostic significance is controversial.

[t\(5;12\)\(q33;p13\)](#)

[t\(5;12\)\(q33;p13\)](#) has been described in MDS and borderline cases between MDS and MPS. Bone marrow eosinophilia and/or monocytosis are predominant features. Cloning of the breakpoints have shown the involvement of an ETS-related gene [TEL/ETV6](#) at 12p13 and the gene for receptor of PDGF β (platelet derived growth factor beta) at 5q33, generating a new transcript from the fusion gene. Variant translocation involving TEL/ETV6 and chromosomes 3, 6 or 10 have been identified and can define a molecular subgroup of MDS with ETV6 rearrangement.

Other 12p changes

MDS presenting with deletion of the short arm of chromosome 12, [del\(12p\)](#) are heterogeneous. Association with multiple karyotypic changes in sMDS is more common than de novo disorders with an 12p- chromosome as a sole aberration. Deletions are usually interstitial, with loss of material between band p11 and p13. FISH method has been used to show that both ETV6 and the gene for an inhibitor of a G1 cyclin-dependant protein kinase ([CDKN1B](#)) are deleted in all myeloid malignancies with a del(12p) including MDS.

[t\(3;5\)\(q25.1;q34\)](#)

Translocation [t\(3;5\)\(q25.1;q34\)](#) is considered as the hallmark of a hematological syndrome presenting as MDS or AML with myelodysplasia. The breakpoints have been characterized at the molecular level and have shown the involvement of [NPM](#) on 5q34 and [MLF1](#) gene on 3q25.1.

[inv\(3\)\(q21q26\)](#) or [t\(3;3\)\(q21;q26\)](#)

An inversion of the long arm of chromosome 3: [inv\(3\)\(q21q26\)](#), or a translocation between both homologous chromosome 3: [t\(3;3\)\(q21;q26\)](#) can be associated with AML or MDS with disturbances of thrombopoiesis expressed by elevated platelet count, dysmegakaryopoiesis (clumps of micromegakaryocytes) and poor prognosis. Transcriptional activation of the [EVI1](#) gene on 3q26 is a consequence at molecular level. Chromosomal changes in addition to the 3q anomalies are frequently demonstrated predominantly aberrations of chromosome 5 or 7.

Rearrangements involving 1q

At least three recurrent unbalanced translocations have been found in primary MDS with a partial trisomy for the long arm of chromosome 1. Such rearrangements are described as [t\(1;15\)\(q11;p11\)](#); [t\(Y;1\)\(q12;q12\)](#); [der\(16\) t\(1;16\)\(q11;q11\)](#).

11q23/MLL-ALL1-HRX gene in MDS

Chromosomal translocations involving [11q23](#) are common in acute monocytic leukemia. A small proportion of hematological neoplasms with 11q23 abnormalities has an initial presentation as MDS, some presenting as sMDS. It can be assumed that some of these translocations are involving [MLL](#), if not all of them. [t\(11;16\)\(q23;p13.3\)](#) involve MLL and [CREBBP](#) and is associated with therapy-related AML

or MDS.

17p- / -17 and p53 mutations

There is an association between vacuolated pseudo-Pelger-Huet granulocytes and chromosome [17p deletion](#) with consistent involvement of [p53](#) gene located at 17p13. It occurs in MDS and AML with poor prognosis. The 17p anomaly is found mainly in sMDS/AML after chemotherapy and/or radiotherapy, usually in association with other complex chromosomal anomalies.

X mutations changes

Pure monosomy X as an acquired abnormality has been sporadically found in female patients with MDS. A typical rearrangement such as an isodicentric chromosome X with breakpoint at q13 has been proposed as typical for acquired sideroblastic anemia with ring sideroblasts. [Xq13](#) may also be involved in translocations in MDS without ring sideroblasts.

del(Y)

The IPSS (International Prognostic Scoring System) considers the [del\(Y\)](#) as a group with a favorable outcome.

To be noted

IPSS (International Prognostic Scoring System) for MDS

RISK FACTORS AND PROGNOSTIC CRITERIA IN MDS: In spite of the longstanding usefulness of the MDS FAB criteria, additional risk classifications including multiple scoring systems, have been used. In order to identify prognosis in MDS and to evaluate their AML transformation, these classifications have included, in addition to the bone marrow blast cell percentage, the bone marrow biopsy features, the degree of specific cytopenias, the age and cytogenetic pattern. Recently an International Prognostic Scoring System (IPSS) has been proposed which takes into account all these parameters. This international MDS risk classification defined four risk sub-groups: low, INT-1, INT-2 and high. The patients are separated for both survival and AML evolution into three prognostic subgroups related to their cytogenetic pattern:

 good (normal, isolated del(5q) alone, isolated del(20q) and -Y ;
 poor (complex abnormalities i.e >3 anomalies) or chromosome 7 anomalies ; and
 intermediate (the remaining cases).

Multivariate analysis combined these cytogenetics subgroups with the percentage of bone marrow blasts and the degree of cytopenia to generate a prognostic model. Stratification for age further improved analysis of survival

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