

# Important Features of Myelodysplastic Syndrome

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## Abstract

Myelodysplastic syndromes (MDS) are characterized by peripheral cytopenias in combination with a hyperplastic bone marrow. During the last 15 years, important progress has been made in the understanding of the biology and prognosis of myelodysplastic syndromes. The classification according to the World Health Organization (WHO) includes mainly morphological criteria and is supplemented by the International Prognostic Scoring System (IPSS) which takes cytogenetical changes into consideration when determining the prognosis of MDS. Also MDS after radiotherapy, chemotherapy or chemical exposure must be distinguished from primary MDS. The underlying mechanisms in primary MDS have not yet been established but it is a multistep alteration to the hematopoietic stem cells that include genes involved in cell cycle control, mitotic checkpoints as well as growth factor receptors, secondary signal proteins and transcription factors which gives the cell a growth advantage over its normal counterpart.

*Key Words:* Apoptosis;Cell cycle control;Clinical features;Mitotic checkpoints;Myelodysplastic syndromes;Transcription factors;Tumor suppressor genes

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## 1. Classification

Peripheral blood cytopenias in combination with a hypercellular bone marrow associated with dysplastic changes are the hallmark of MDS. In 1982, the French-American-British (FAB) Cooperative Group classified five subentities of MDS [1]: refractory anemia (RA), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEB-T), refractory anemia with ringed sideroblasts (RARS), and chronic myelomonocytic leukemia (CMML). This classification was recently revised resulting in the WHO-classification (Table 1) [2,3]. The initial chromosomal aberration, the age of patient and the number and severity of cytopenias are important to evaluate the prognosis of MDS as summarized in the International Prognostic Scoring System (Table 2) [4]. The survival of MDS patients according to this classification ranges from 6 years for low-risk patients to 6 months for high-risk individuals.

Myelodysplastic syndromes occur primarily in the el-

derly population, with a median age between 60 and 75 years, and an incidence of about one of 500 individuals over the age of 60 [5]. Despite this predominance of elderly individuals, MDS has occasionally been reported in those who are younger and even in children. In recent years, the incidence of MDS appears to be rising, due possibly to increased diagnostic awareness. The sex distribution is balanced [5], despite earlier reports indicating a male preponderance. The exception is CMML, which has a clear male preponderance [6].

Secondary MDS (changes in hematopoiesis after radiotherapy, chemotherapy or chemical exposure) must be distinguished from primary "de novo" MDS without specific history. Secondary MDS has been described following therapy of malignancies (e.g. Hodgkins disease, non-Hodgkin lymphomas, multiple myeloma) [7-9]. Alkylating chemotherapy are implicated as the causative agent most frequently [10]. The highest incidence of secondary MDS is 2 to 4 years after treatment of the antecedent malignancy [11]. Furthermore, secondary MDS is an important and frequent late complication of potentially

**Table 1.**

World Health Organization Classification of MDS.

Category	Peripheral blood	Bone marrow
1a. RA without dysplasia	Blasts <1% Mono <1,000/ $\mu$ L	Blasts <5% Ringed sid. <15%
1b. RA with dysplasia	Same+dysgranulocytes and/or giant platelets	Same+dysgranulocytes and/or dysmega
2a. RARS without dysplasia	Blasts <1% Mono <1,000/ $\mu$ L	Blasts <5% Ringed sid. 15%
2b. RARS with dysplasia	Same+dysgranulocytes and/or giant platelets	Same+dysgranulocytes and/or dysmega
3a. RAEB-I	Blasts 1-5 % Mono <1,000/ $\mu$ L	Blasts 5-10 %
3b. RAEB-II	Blasts 6-20 % Mono <1,000/ $\mu$ L	Blasts 11-20 %
4. CMML*	Blasts <1-20 % Mono >1,000/ $\mu$ L	Blasts 0-20 %

RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; CMML, chronic myelomonocytic leukemia; Mono, monocytes; Sid., sideroblasts; Dysmega., dysmegakaryocytes. \*when white blood cell count >13,000/ $\mu$ L, list under myeloproliferative disorders.

**Table 2.**

International Prognostic Scoring System for MDS.

Score value*	Bone marrow blasts (%)	Karyotype	Cytopenias (lineages affected)
0	<5	Normal, -Y, del 5q, del 20q	0 to 1
0.5	5-10	Others	2 to 3
1.0		Complex** and/or chromosome 7 anomalies	
1.5	11-20		
2.0	21-30		

\*The prognostic score is determined by the sum of the single scoring values. The risk groups are determined as follows (brackets: median survival):

Low-risk: 0 points (5.7 years).

Intermediate-1-risk: 0.5-1.0 points (3.5 years).

Intermediate-2-risk: 1.5-2.0 points (1.2 years).

High-risk:  $\geq$ 2.5 points (6 months).

\*\* $\geq$ 3 chromosomal abnormalities.

curative hematopoietic stem cell transplantation [12-14].

Secondary MDS is also associated with occupational and environmental risk factors such as exposure to organic compounds (benzene), oil, solvents, ammonia and pesticides as well as smoking, working in agriculture or textiles [15-17]. Ionizing irradiation clearly increases the risk of development of MDS/AML [18]. The incidence of MDS/AML after 400 rad or less exposure from the Hiroshima nuclear explosion produced approximately two

cases of MDS/AML per 10<sup>6</sup> persons/year/rad.

## 2. Clinical Features

Fatigue and exertional dyspnea may develop over a prolonged period of time often exceeding 6 to 12 months, and may be misinterpreted as either cardiac failure or pulmonary disease particularly in elderly individuals. Approximately half of the patients are asymptomatic at the time of initial diagnosis and the disease is usually found after a routine blood count. Progressive hematopoietic failure leading to anemia, thrombocytopenia and leukopenia, either alone or in any combination, is the dominant finding in MDS. Anemia is an almost universal characteristic at the time of initial diagnosis, with more than 80% of patients presenting with a hemoglobin concentration below 10 g/dL. The reticulocyte count usually is reduced.

The peripheral blood leukocyte count is usually normal or low. Although leukopenia is seen in only 25 % to 30 % of patients with MDS, the percentage varies between 40 % in cases with RAEB and 80 % in those with RAEB-T, increasing with the degree of blast cell replacement of the bone marrow. Granulocytes may morphologically have a reduced segmentation or reduced to absent granulation. Myelocytes and blasts may be present in the blood smear, the latter being used for classification. In a detailed history, approximately one third of the individuals report recurrent infections. These occur not only because of granulocytopenia but also as a result of defects of neutrophil function (impaired chemotaxis, reduced phagocytic activity).

Signs of bleeding, mainly petechiae, gingival bleeding, or hematoma following trivial injuries, are surprisingly

uncommon, given the frequency of thrombocytopenia. Fewer than 10% of patients will present initially with serious bleeding, e.g. gastrointestinal hemorrhage, macrohematuria, retinal or central nervous system hemorrhage.

### 3. Genetic and Molecular Changes and Possible Disease Mechanisms

Both structural and numerical cytogenetic changes may be found in primary MDS (reviewed by Mecucci 1999 [19] and Fenaux 1996 [20]). The most frequent chromosomal abnormalities in MDS involve chromosomes 5, 7, 8, 11, 12, and 20. The incidence of chromosomal abnormalities in secondary MDS is higher and more complex, and more frequently involves the long arms of chromosomes 5 and 7 (Table 3).

The underlying mechanisms in primary MDS have not yet been established. G6PD studies and RFLP have shown that MDS is a clonal abnormality of the hematopoietic stem cell characterized by defective maturation and in advanced stages uncontrolled proliferation [21]. Studies using cytogenetical markers suggest that the lymphocytes are not involved in the clonal hematopoiesis in MDS [22]. The preponderance of evidence suggests that MDS results from a multistep process including initial insults to the hematopoietic stem cells by a toxin or spontaneous mutation followed by additional alterations of cell cycle control genes, mitotic checkpoint genes, transcription factors as well as known tumor suppressor genes (Table 4).

The clinically distinct entity of 5q- syndrome involves a deletion of the long arm of chromosome 5 and is characterized by a female preponderance, thrombocytosis, macrocytic, fairly severe anemia often requiring red blood cell (RBC) transfusions, prominent megaloblastoid erythroid hyperplasia in the bone marrow, and megakaryocytes which are unusually large, often greater than 30  $\mu$ m in diameters and which often have a single eccentric round nuclei [23]. Interestingly, the rate of leukemic transformation in individuals with 5q- syndrome is only 25 % after an observation period of 15 years [4]. The underlying molecular lesions in 5q- syndrome is still unknown. The critical segment may be

at chromosome 5q31 [24,25]. The human GRAF gene located in this region can fuse to the MLL gene disrupting both alleles [26], but the significance of this gene in the 5q- syndrome is unclear.

In striking contrast to this syndrome is the occurrence of loss of chromosome 5 or 5q- in therapy-related MDS which presages an almost inevitable leukemic transformation. This may be associated with loss of other regions of 5q compared to the region in the 5q- syndrome.

One reason for the abnormal proliferation which is associated with a block of differentiation in MDS may be the disturbance of mitotic checkpoint proteins [27]. Checkpoint pathways control the order and timing of cell cycle transitions and ensure that critical events, such as DNA replication and chromosomal segregation, are completed with high fidelity [28]. Elimination of checkpoints may result in cell death, infidelity in the distribution of either chromosomes or other organelles between dividing cells, or increased susceptibility to environmental perturbations such as DNA damaging agents. This can result in abnormal cell growth as observed in MDS.

Other abnormalities include changes in genes which regulate the cell cycle like the cyclin dependent kinase inhibitors (CDKI). Transcription of these gene can be silenced due to abnormal methylation of their promoter regions [29-31], mutations or deletions of the gene or conformation changes of the genomic DNA caused by histone deacetylation. Genetic instability as detected by microsatellite instability in early MDS may also contribute to the clonal expansion of the MDS cells [32]. One study suggested that a disproportionate number of individuals who develop therapy-related MDS/AML have a germline mutation of one of their mismatch repair genes making them predisposed to MDS/AML after toxic exposure [33]. However, other studies have been unable to substantiate these findings [34-36].

Known abnormalities include point mutations of RAS (frequency of 10-15 %) and alterations of RB1 and p53 (5 and 10%, respectively). Concerning the RAS genes in MDS, N-RAS is most frequently mutated, with a point

**Table 3.**

Most Frequent Chromosomal Aberrations in MDS Patients.

Numerical	Translocations	Deletions
+8 (19 %)	inv 3 (7 %)	del 5q (27 %)
-7 (15 %)	t(1;7) (2 %)	del 11q (7 %)
+21 (7 %)	t(1;3) (1 %)	del 12q (5 %)
-5 (7 %)	t(3;3) (1 %)	del 20q (5 %)
	t(6;9) (<1 %)	del 7q (4 %)
	t(5;12) (<1 %)	del 13q (2 %)

Frequency of chromosomal aberration is given in brackets. -, loss of chromosome; +, additional chromosome; inv, inversion; t, translocation; del, deletion.

**Table 4.**

Molecular Defects in MDS.

Gene	Type of alteration	Frequency
p53	Mutation	27/252 (11 %)
CHK2	Mutation	1/41 (3 %)
p14 <sup>ARF</sup>	Promoter methylation	4/60 (7 %)
p15 <sup>INK4b</sup>	Promoter methylation	36/85 (42 %)
NRAS	Mutation	37/345 (11 %)
RB1	Mutation	2/37 (5 %)

p53, tumor protein p53; CHK2, checkpoint kinase gene CHK2; p14<sup>ARF</sup>, cyclin-dependent kinase inhibitor 2A; p15<sup>INK4b</sup>, cyclin-dependent kinase inhibitor 2B; NRAS, oncogene NRAS; RB1, retinoblastoma gene 1

mutation occurring at either codon 12, 13 or 61. Mutations of this gene result in an activated protein which stimulates its downstream targets such as RAF and MAPK. MDS with mutant N-RAS may be associated with a worse prognosis [37]. Activation of the RAS pathway is most frequently associated with an abnormality that has a monocytoid-like differentiation.

Alterations of the p53 gene occur in about 10% of individuals with MDS. Changes are usually missense mutations of one allele with the second allele being lost. Patients whose abnormal clone is marked by an isochromosome 17q, often have a p53 mutation in these cells. The mutation usually prevent the protein from being able to bind to DNA thus losing its ability to transactivate target genes such as the cyclin dependent kinase inhibitor (CDKI) p21<sup>WAF2</sup>. Mutations of p53 are associated with progression of the disease and poor prognosis. Recently, somatic point mutations of several myeloid transcription factors have been demonstrated in patients with AML and MDS including AML-1 and C/EBP $\alpha$  [38-40].

At the early stage of the disease, normal hematopoiesis will be coexistent with the abnormal hematopoietic clone, but the malignant cells may produce inhibitory proteins which block differentiation of the normal cells such as tumor necrosis factor alpha [41]. Furthermore, increased apoptosis of the bone marrow cells may also contribute to ineffective hematopoiesis [42]. Also, the MDS clone may have a defective response to growth factors due to aberration of growth factor receptors or post-receptor signal transduction pathways [43].

#### 4. Differential Diagnosis

The clinical diagnosis of typical MDS according to FAB criteria is often straightforward and presents no difficulty. While the diagnosis may be suspected on the basis of the history and the peripheral blood findings, morphological examination of the bone marrow is essential to establish the diagnosis. Exclusion of hypoplastic/aplastic anemia may be difficult in hypocellular MDS. Rarely, disorders with hypoplastic hematopoiesis, e.g. amegakaryocytic thrombocytopenia, chronic neutropenia, and aplastic anemia can evolve into acute leukemia and must be distinguished from MDS. In these cases, chromosomal abnormalities may be helpful to verify MDS.

Furthermore, serum vitamin B<sub>12</sub> and folate levels are often measured to exclude these vitamin deficiency. In young patients, congenital dyserythropoietic anemias and pure red cell anemia must be considered, the latter can be associated with MDS [44]. Sideroblastic changes may also be caused by drugs (chloramphenicol, tuberculo-static agents, penicillamine), alcohol, and occupational toxins (lead, benzene), or be associated with nonmalignant disorders (renal or hepatic failure, connective tissue disease).

Individuals infected with human immunodeficiency virus can have morphological features of MDS in their bone marrow and they have to be distinguished from

primary MDS. Disorders that result in peripheral destruction of the mature cells (immune phenomena, infectious agents, mechanical hemolysis, hypersplenism) must be excluded. The distinction between CMML and chronic myelogenous leukemia (CML) can sometimes present diagnostic difficulties. Cytogenetic (Philadelphia chromosome) and molecular (bcr/abl-translocation) studies will help in such cases. On the other hand, the distinction between osteomyelofibrosis and MDS with accompanying myelofibrosis can be difficult.

Recently, we and others have shown that microarray analyses can provide sufficient data to detect genes or gene patterns which are associated with alterations of specific cellular pathways or signal cascades in tumor cells [45-49] including myelodysplastic syndromes [50,51]. The technique of gene expression profiling can also be used for subclassification of leukemias [52] and lymphomas [53]. The approach to predict prognosis or risk type of MDS using gene expression data, is a long way from practice; but the ability to predict who will do well and who will not, may have a strong impact on the further classification and risk definition of MDS.

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