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Recent Advances in Myelodysplastic Syndromes

Guest Editors: Miguel Angel Sanz, Guillermo Sanz & Teresa Vallespí

Diagnosis, classification, and cytogenetics of myelodysplastic syndromes

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ABSTRACT

Background and Objective. **The diagnosis of myelodysplastic syndromes (MDS) is essentially morphological and based on the presence of dysplastic features in the peripheral blood and bone marrow. The French-American-British (FAB) Cooperative Group proposed a classification based on easily obtainable laboratory information. In spite of some limitations, the FAB criteria have been useful for a long time. Currently, the recognition of other distinct morphological MDS subgroups such as hypocellular MDS and MDS with myelofibrosis, the increasing incidence of MDS in children as well as that of therapy-related MDS, and the finding of specific chromosomal alterations associated with different morphological features, reveal the insufficiency of this classification. The aim of the present review is to examine some new aspects of the diagnosis, classification, and cytogenetics of MDS.**

Evidence and Information Sources. **The authors of this review have been actively working and contributing original papers on MDS for the last 15 years. They also organized or participated in the Fourth International Symposium on MDS (Barcelona, April 24-27, 1997). In addition, the present review critically examines relevant articles and abstracts published in journals covered by the Science Citation Index© and Medline©.**

State of the Art and Perspectives. **Most of investigators working on MDS tend to integrate morphology and cytogenetics in the diagnosis and classification of these disorders. FAB criteria remain useful particularly for patients with not available cytogenetic study. Refractory cytopenia with multilineage dysplasia should be considered as a new MDS subtype. Some authors propose considering all patients with more than 20% of blast cells in peripheral blood or bone marrow as having acute leukemia. Chronic myelomonocytic leukemia with myeloproliferative features may be included among chronic myeloproliferative disorders. MDS with myelofibrosis is recognized as a new MDS subtype. Therapy-related MDS (t-MDS) should be classified according to the involved agents. Finally, besides including chromosomal abnormalities in the diagnosis (e.g., RAEB with trisomy 8), several cytogenetic abnormalities such as deletion 5q and deletion 17p, associated to specific clinical-morphological features, should be of help to identify new MDS syndromes.**

Key-words: dyshemopoiesis, FAB subtypes, chromosome changes, MDS

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The diagnosis of myelodysplastic syndrome (MDS) requires a careful light microscopic examination of optimally stained peripheral blood and bone marrow smears and trephine biopsy sections, with the diagnosis being based on the presence of dysplastic features of hematopoietic lineage. Abnormalities such as erythroblasts with abnormal nuclear shape, ringed sideroblasts, degranulation/hyposegmentation of granulocytes, large-degranulated platelets and micromegakaryocytes in a patient with unexplained cytopenia are characteristic features of MDS.[1,2]

In spite of some limitations, The French-American-British (FAB) Cooperative Group classification for MDS[3] has been useful for the last fifteen years. At present, the recognition of other distinct subgroups such as hypocellular MDS and MDS with myelofibrosis, the increasing incidence of MDS in children as well as that of therapy-related MDS, and the finding of specific cytogenetic abnormalities make necessary to review this classification.[1,2,4]

Cytogenetic studies in MDS may have pathogenetic, diagnostic, and prognostic implications. The cytogenetic study of bone marrow cells is mandatory in the diagnosis and classification of MDS, with the most frequent chromosome abnormalities being del(5q), monosomy 7, trisomy 8 and complex karyotype.[5] Conventional cytogenetics methods are routinely used to detect karyotypic abnormalities in the

bone marrow cells of MDS patients. Nevertheless, these techniques have several drawbacks, the most important being that cytogenetic analyses are limited to metaphases.[6] Fluorescent *in situ* hybridization (FISH) method, using chromosome-specific DNA probes, allows the detection of chromosomal abnormalities in interphase nuclei and metaphase chromosomes.[7] FISH has been found to be particularly useful to determine the number of cells with a specific chromosomal abnormality and identify the origin of aberrant or marker chromosomes.[6-9] An additional problem is the identification of the cell lineage bearing cytogenetic abnormalities. Combined immunophenotyping and FISH techniques make possible to identify the nature of the cell with chromosomal aberrations and the number of lineage involved.[9,10] For all these reasons, conventional cytogenetic analysis should be completed (but no replaced) in most cases by FISH and, occasionally, by combined FISH and immunophenotypic or cytochemistry analyses.

Diagnosis

The diagnosis of MDS is essentially morphological and is based on the presence of dysplastic features in peripheral blood and bone marrow (Table 1). Bone marrow dyspoiesis results in cytopenia probably due to an increased apoptosis of the bone marrow dyshemopoietic cells.[11]

The most reliable features of MDS include the presence of micromegakaryocytes in bone marrow, trilineage dysplasia, a high percentage of blasts cells, or cytogenetic abnormalities. Nutritional deficiencies, drug-induced dyshematopoiesis, alcoholism, anemia of chronic diseases, and metabolic disturbances accompanying chronic renal and liver diseases should be excluded before accepting the diagnosis of MDS.[2]

Dyshemopoietic morphological features (Figures 1-12)

Dyserythropoiesis

This is characterized by the presence of anisocytosis, prominent macrocytosis, basophilic stippling, poikilocytosis, nucleated red blood cells, and acanthocytosis in peripheral blood. In bone marrow, dyserythropietic changes include megaloblastosis and nuclear abnormalities (e.g., multinuclearity, nuclear fragments, bizarre nuclear shapes, abnormal mitosis, internuclear bridging[12] and abnormal dense chromatin); cytoplasmic abnormalities may include Howell-Jolly bodies, intense cytoplasmic basophilia, defects in hemoglobinization and ghosted cytoplasm (erythroblasts with areas of unstained cytoplasm). These erythroblasts with ghosted cytoplasm coexisting with coarse basophilic stippling (May-Grünwald-Giemsa stain) seem to represent ringed sideroblasts.[13] Iron staining in bone marrow may show the presence of ringed sideroblasts that are the result of iron deposition in the mitochondria. This abnormality is important since the proportion of ringed sideroblasts (>15%) defines a subgroup of MDS (refractory anemia with ring sideroblasts). Nevertheless, ringed sideroblasts may be found in other MDS subgroups, although in a lower proportion.[14]

Dysgranulopoiesis

This is easily recognized in peripheral blood, with the most common findings being hypogranulation and hyposegmentation (i.e., Pelger-Huët-like anomaly). In fact, a very good correlation between the degree of hypolobulation and/or hypogranulation in peripheral blood and that observed in bone marrow has been found.[15] Abnormal chromatin clumping is another morphological feature seen in MDS; it may be associated with granulocytic hyperplasia in bone marrow and leukocytosis. Granulocytes with a nuclear hole (i.e., ring-shaped nuclei) may be present. Persistent associated basophilia of the rim and excess of azurophilic granulation or granules larger than usual can also be found. Nuclear sticks can be seen particularly in cases of secondary MDS or therapy-related MDS.[4]

Dysmegakaryocytopoiesis

The most common dysplastic features in the megakaryocytic lineage are the presence of micromegakaryocytes, large mononuclear forms and megakaryocytes with multiple small nuclei. Megakaryocytes with non-lobulated nucleus (i.e., large mononuclear forms) are typical of the 5q- syndrome. Platelets are also affected by the dyspoietic changes with a high number of giant or degranulated platelets.

Table 1. Morphological features of MDS.

PB	BM
Dyserythropoiesis	
Anisocytosis	Multinuclearity
Poikylocytosis	Abnormal nuclear shape
Macrocytosis	Megaloblastoid changes
Basophilic stippling	Cytoplasmic abnormalities
Nucleated RBC	Ringed sideroblasts
*Dysgranulopoiesis**	
Pelger-Huët-like anomaly	Clumping of chromatin
Degranulation	Larger granules
Hypersegmentation	Ring-shaped nuclei
Nuclear sticks	
Döhle bodies	
Dysthrombopoiesis	
Large platelets	Micromegakaryocytes
Hypogranulation	Large mononuclear forms
Hypergranulation	Multiple small nuclei

**All dysgranulopoietic features can be analyzed in peripheral blood (PB) or in bone marrow (BM).*

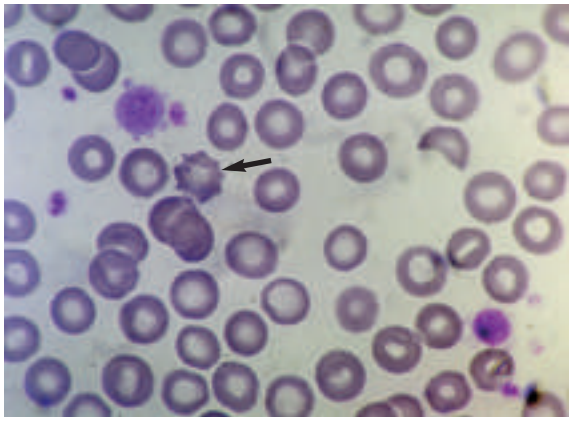

Figure 1. Peripheral blood. Besides large platelets, an achantocyte (arrow) may be observed.

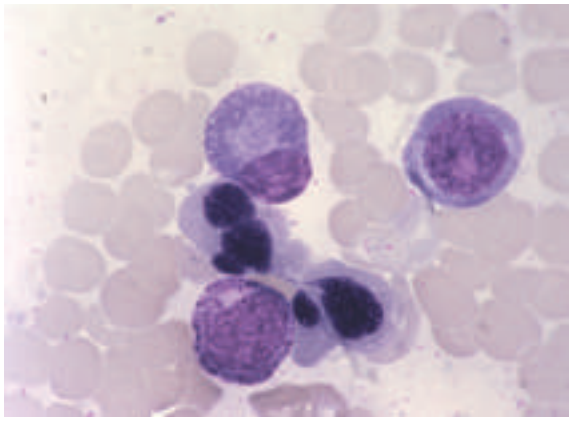

Figure 2. Bone marrow. Dyserythropoietic features: abnormalities in nuclear shape and internuclear bridge.

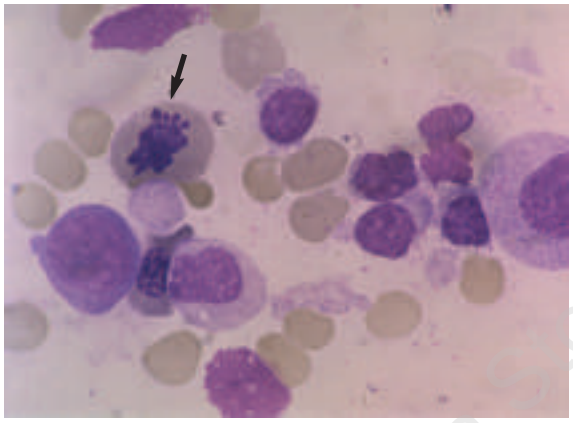

Figure 3. Bone marrow. An abnormal erythroblast with basophilic stippling is present (arrow).

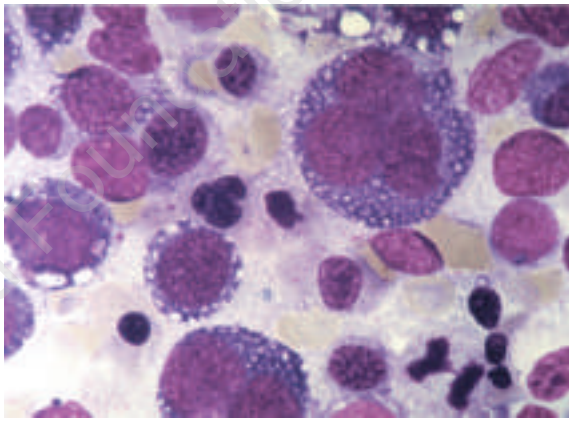

Figure 4. Bone marrow. Dyserythropoietic features consisting in multinuclearity, an abnormal mitosis, and cytoplasm vacuolization are present.

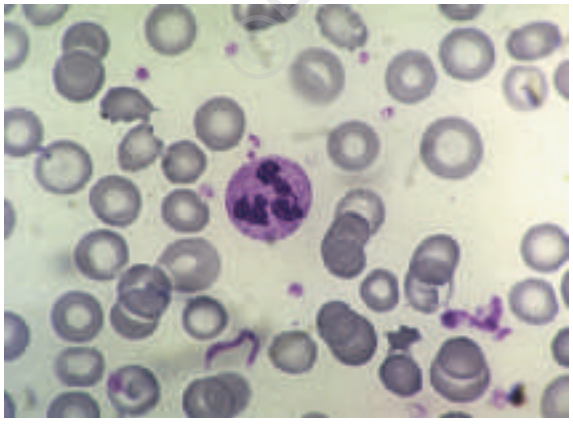

Figure 5. Peripheral blood. Hypersegmented granulocyte.

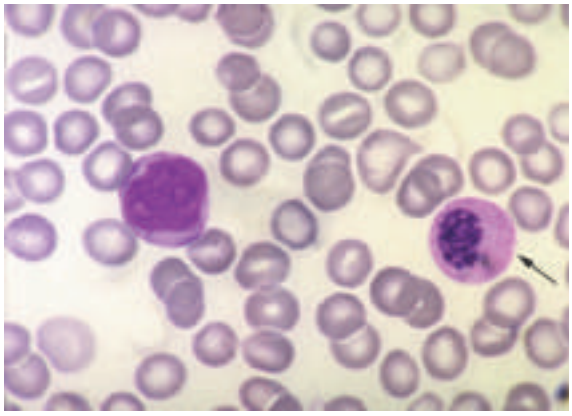

Figure 6. Peripheral blood. A blastic cell and a a neutrophil with pseudo Pelger-Huët characteristics (arrow) are present.

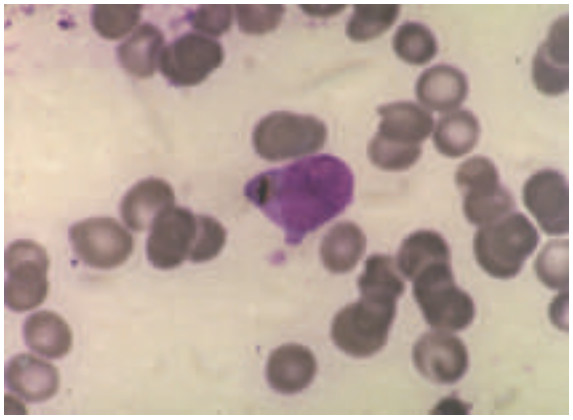

Figure 7. Bone marrow. Blast cell with an Auer rod (peroxidase staining).

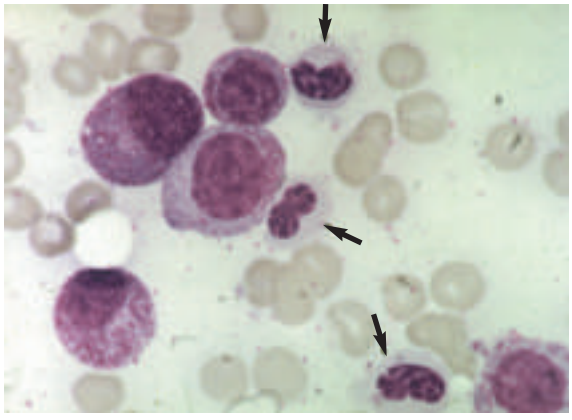

Figure 8. Bone marrow. Degranulation and abnormal chromatin clumping in leukocytes (arrows).

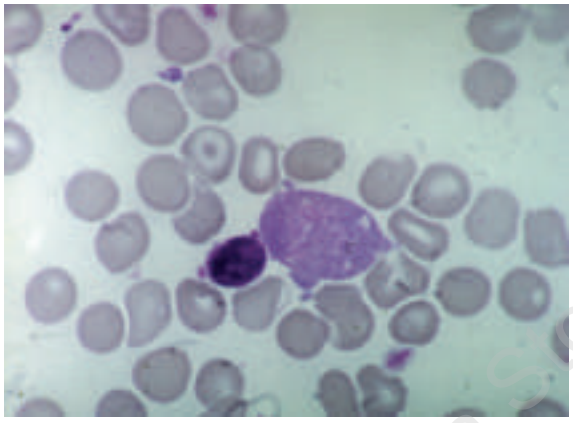

Figure 9. Peripheral blood. Giant and dysmorphic platelet and a micromegakaryocyte.

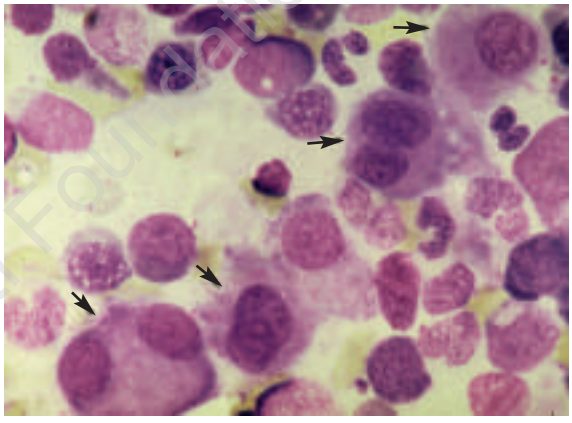

Figure 10. Bone marrow. Micromegakaryocytes (arrows).

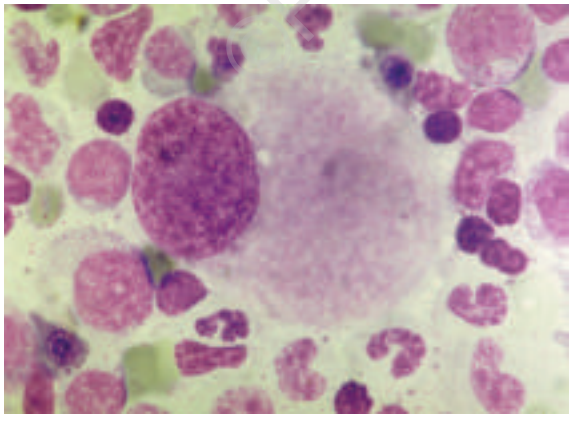

Figure 11. Bone marrow. Large hypolobulated megakaryocyte.

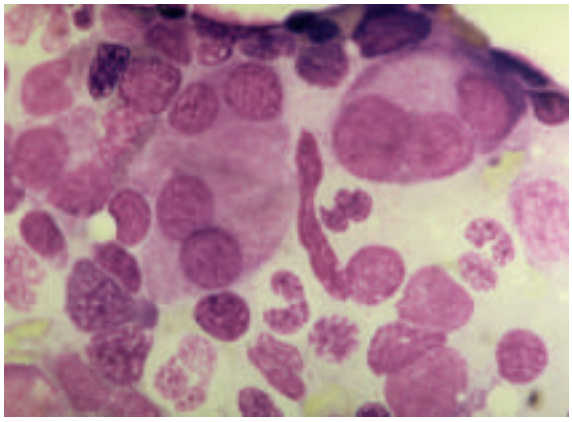

Figure 12. Bone marrow. Megakaryocytes with multiple small nuclei.

Blast cells characteristics

The FAB group established criteria to define two types of blast cells. Type I blast is a primitive cell without granules and with one or two nucleoli. Type II blast is slightly larger and has at least one azurophil granule. Some authors have proposed a third type of blast cell: namely, those with more than 20 azurophilic granules in the cytoplasm and not displaying a Golgi zone.[16]

Bone marrow histology

Bone marrow biopsy provides an excellent appreciation of the cellularity and may be especially valuable in the diagnosis of hypocellular MDS. The presence of immature cells located centrally in the medullary tissue instead of lining the endosteal surface (i.e., ALIP, *abnormal localization of immature progenitor cells*) has been suggested to be of clinical relevance, particularly if they are of myeloid nature.[17] Reticulin fibers are increased in many patients with MDS. However, severe bone marrow fibrosis is rare and, if present, it is associated with a rapidly progressive clinical course. In addition, the proportion of megakaryocytes and their morphology are best evaluated on trephine sections.

Classification of MDS

Since 1938, when Rhoads and Barker used the term refractory anemia to describe a group of anemic disorders of unknown etiology for which no effective treatment was available,[18] several different designations have been employed to define entities belonging to this spectrum of disorders (Table 2).[19]

In 1982, the FAB Cooperative Group proposed a classification based on easily obtainable laboratory data. According to the presence of dysplastic features, the percentage of blast cells in peripheral blood and bone marrow, the presence of Auer rods, the absolute blood monocytosis, and the percentage of ringed sideroblasts, the FAB group distinguished the following MDS types (Table 3): 1) refractory anemia (RA); 2) refractory anemia with ring sideroblasts (RAS); 3) refractory anemia with excess of blasts (RAEB); 4) chronic myelomonocytic leukemia (CMML); and 5) RAEB *in transformation* (RAEB-t).[3] This classification has been widely accepted.

Refractory anemia (RA) or refractory cytopenia

The main presenting feature is anemia with a low reticulocyte count. However, since in most instances anemia is typically accompanied by neutropenia and/or thrombocytopenia a better term would be *refractory cytopenia*.[4] Besides the characteristics shown in Table 1, the bone marrow usually displays dyserythropoiesis, either alone or with dysgranulopoiesis and dysmegakaryocytopoiesis; some cases may also present red cell hypoplasia.

Refractory anemia with ring sideroblasts (RAS)

The major difference between RA and RAS is the presence of ringed sideroblasts accounting for more than 15% of nucleated red cells (polychromatic and orthocromatic erythroblasts) in the bone marrow.[20] The natural history of RAS is characterized by an initial phase of erythroid hyperplasia and ineffective erythropoiesis, which is usually stable for many years but in a subset of patients may be followed by a phase of marrow failure with or without transformation into acute leukemia.[21] Two types of RAS have been distinguished: 1) *pure sideroblastic anemia* (PSA), which only shows signs of dyserythropoiesis in the bone marrow and has a very low propensity to evolve into acute leukemia and has a relatively good prognosis; and 2) *refractory anemia with ring sideroblasts* (RARS), charac-

Table 2. Chronology and terminology of myelodysplastic syndromes.[19]

Term	*Year*	*Author*
Refractory anemia	1938	Rhoads & Barker
Preleukemic anemia	1949	Hamilton-Paterson
Preleukemia	1953	Block et al.
Refractory anemia with ringed sideroblasts	1956	Björkman
Refractory normoblastic anemia	1959	Dacie et al.
Smoldering acute leukemia	1963	Rheingold et al.
Chronich erythremic myelosis	1969	Dameshek
Preleukemic syndrome	1973	Saarni and Linman
Subacute myelomonocytic leukemia	1974	Sexauer et al.
Chronic myelomonocytic leukemia	1974	Miescher & Farquet
Hypoplastic acute myelogenous leukemia	1975	Beard et al.
Refractory anemia with excess of myeloblasts	1976	Dreyfus
Hematopoietic dysplasia	1978	Linman & Bagby
Subacute myeloid leukemia	1979	Cohen et al.
Dysmyelopoietic syndrome	1980	Streuli et al.
Myelodysplastic syndromes	1982	Bennett et al.

Table 3. Myelodysplastic syndromes: FAB criteria.

	RA	*RAS*	*RAEB*	*CMML*	*RAEB-t*
Blood					
Cytopenia(s)	+	+	+	+	+
Monocytes			$\geq 1\times10^9$/L		
Blasts (%)	< 1	< 1	< 5	< 5	≥ 5
Bone marrow					
Blasts (%)	< 5	< 5	5–20	0–20	21–30
Auer rods	–	–	–	–	+
Dysmyelopoiesis	+	+	+	+	+
Ring–sideroblasts (%)	≤ 15	> 15			

RA: refractory anemia; RAS: refractory anemia with ring sideroblasts; RAEB: refractory anemia with excess of blasts; CMML: chronic myelomonocytic leukemia; RAEB–t: refractory anemia with excess of blasts "in tranformation".

terized by the presence of dysgranulopoiesis and/or dysmegakaryopoiesis in addition to dyserythropoiesis, which has a higher risk of leukemic transformation, and a shorter survival.[22,23] In the Spanish Cooperative Group experience, only the hemoglobin level (< 80 g/L) and the platelet count (< 100×10^9/L) were found to be of value to separate different risk groups among RAS patients.[24] Nevertheless, a recent study in a large series of RAS patients (69 PSA vs. 120 RARS) shows significant differences between both subtypes. Thus, PSA patients showed higher neutrophil and platelet counts, less chromosome abnormalities, lower risk of acute leukemia transformation and higher rate of survival than patients with RARS.[25]

Refractory anemia with excess of blasts (RAEB)

In contrast with RA and RAS, dysgranulopoiesis is a predominant feature in RAEB. Another characteristic is the frequent presence of micromegakaryocytes. Ringed sideroblasts, and reflecting dyserythropoiesis, may also be found.

RAEB in transformation (RAEB-t)

This is a transitional subtype between RAEB and acute leukemia. Whether cases with Auer rods in granulocyte precursors should be considered as RAEB or as RAEB-t is controversial. While some authors find no differences between Auer-positive and Auer-negative RAEB subgroups,[26] others consider cases with Auer rods as AML.[27] In a report, MDS with Auer rods was found to be closer to RAEB-t and, accordingly, to acute leukemia than to RAEB.[28] In the MD Anderson experience, patients classified as RAEB-t on the sole basis of the presence of Auer rods (4 RA/RAS; 6 CMML; and 19 RAEB) had a median survival longer than the other RAEB-t patients. Moreover, these 19 patients who, without Auer rods, would be considered RAEB had a higher probability of survival than RAEB patients as conventionally defined. Furthermore, patients with RAEB-t, by blood or marrow blast criteria, and Auer rods were more likely to live longer than those with RAEB-t without Auer rods. Besides, 10% of patients with RAEB-t and Auer rods showed karyotypes associated with good prognosis: such as inv(16)/t(8;21).[29] It is likely that most cases of RAEB-t represent truly acute leukemias rather than MDS.

Chronic myelomonocytic leukemia (CMML)

The defining feature of CMML is the absolute monocytosis (>1×10^9/L) in peripheral blood, often associated with an increase in the number of leukocytes and the presence of immature myeloid and erythroid precursors. Whether CMML should be considered a MDS is controversial because it shares many characteristics with myeloproliferative disorders (e.g., hepatosplenomegaly, leukocytosis and occasionally marrow fibrosis). In fact, Shepherd *et al.* consider CMML as a subtype of chronic myeloid leukemia (CML).[30] On its turn, Martiat *et al.* found that *m-bcr*-negative CML resembled CMML in its cytogenetic and myelodysplastic features and proposed that both disorders should be regarded as two states of the same disease.[31] On the other hand, the fact that some MDS evolve into CMML, with or without a subsequent transformation into acute leukemia, would support their inclusion within the MDS.[32] The FAB group has suggested to segregate two CMML subtypes: myelodysplastic-CMML (WBC count: < 13×10^9/L) vs. myeloproliferative-CMML (WBC count: ≥ 13×10^9/L).[33] Recent studies comparing MDS-CMML and MPD-CMML found some clinical (e.g., shorter survival and higher risk of acute transformation in MDS-CMML) and biological (e.g., higher bilirubin levels and more frequency of abnormal karyotype for MDS-CMML patients) differences between the two subtypes of CMML. However, in most cases overlapping forms predominate.[34,35] In addition, CMML displays a biologic feature useful to distinguish it from other MDS types which consists of the excessively increased growth of CFU-GM in the absence of supplementation with an exogenous source of colony-simulating activity.[36]

Finally, some authors suggest that MDS with monocytosis (> 10% of monocytes in peripheral blood; CMML patients excluded) should be considered as a distinct subset of MDS characterized by multi-lineage dysplasia and a higher incidence of karyotype aberrations.[37] Clearly, a more refined definition of CMML and its different subtypes is required.

Future trends

During many years the FAB classification has provided a common language for physicians and has also given important prognostic information as well as a framework for studying MDS. However, in some cases MDS can not be classified on the sole basis of morphological features. Whenever possible, morphological characteristics should be integrated with other parameters such as cytogenetic and molecular studies in order to gain insight into the origin of MDS and eventually to provide a more accurate diagnosis. In this context, there are a number of new proposals arising to improve FAB classification, some of these are summarized in Table 9.

Other MDS subgroups

Refractory cytopenia with multilineage dysplasia (RCMD)

This is a MDS with bi-cytopenia or pancytopenia in peripheral blood and dysplastic changes in more than one cell line. No or occasional blasts in blood, no increased bone marrow blasts and absence of Auer rods are other characteristics of this subtype. Cytogenetic abnormalities are similar to those found in RAEB.[38,39]

Hypocellular MDS

Although most MDS patients present with a hypercellular or normocellular bone marrow, a number of patients may have hypoplasia at diagnosis.[39] The

reported incidence of hypoplastic forms varies from 7% to 19%. MDS is considered hypocellular when the cellularity in the bone marrow biopsy is less than 30% 40 or less than 20% when the patient is more than 60 years old.[41] The identification of dysmyelopoietic features can be difficult to identify when the bone marrow cellularity is low. Under these circumstances, the bone marrow biopsy may be useful to establish the diagnosis of hypocellular MDS by disclosing a disturbed architectural pattern, reticular fibrosis and abnormal megakaryopoiesis.[42] Although they are not a constant finding, karyotype abnormalities, particularly those involving chromosome 7, seem to be associated with hypoplastic MDS.[43] Since patients with otherwise typical aplastic anemia and clonal cytogenetic abnormalities have an especially high risk of developing MDS, the presence of associated clonal cytogenetic alterations would suggest hypocellular MDS rather than aplastic anemia (AA).[44] In recent studies, using immunostaining of bone marrow biopsy specimens, hypocellular MDS cases showed higher number of megakaryocytes,[45] higher values of PCNA (i.e., proliferating cell nuclear antigen) and higher percentage of CD34 cells as compared to AA cases.[46] There is no consensus in the prognosis of this special subgroup of MDS. Whereas some investigators have reported that these patients are less likely to progress to AML and have longer survival than in classic MDS,[40] others have not confirmed this notion.[41] Clinical, hematological, and cytogenetic features do not differ significantly from other MDS.[43,47] Tuzuner *et al*. propose to not segregating hypocellular MDS from the FAB classification because, in their experience, patients with hypocellular MDS have similar clinical/morphological features and prognosis than those with normo/hypercellular MDS.[48]

MDS with myelofibrosis

The incidence of myelofibrosis in primary MDS has been extensively evaluated, ranging from 17 to 47%.[49,50] Myelofibrosis may be observed in all MDS subtypes, with a higher frequency in chronic myelomonocytic leukemia.[49,50] The fibrosis is generally described as slight or moderate. Major fibrosis with occasional collagen deposits is encountered in less than 10% of the cases.[50]

Initially described by Sultan *et al*.,[51] MDS with myelofibrosis is characterized by pancytopenia, minimal organomegaly, hypercellular bone marrow with marked fibrosis, trilineage dysplasia, and atypical megakaryocytic proliferation with a predominance of small forms with hypolobulated nuclei.[39] The dysplastic features of the erythroblastic and granulocytic series are similar to those observed in other MDS. However, abnormalities of the megakaryocytic series are often marked. Two main aspects may be observed. First, a predominance of dwarf megakaryocytes with scant cytoplasm, hypolobulated nucleus and coarsely stippled chromatin; the myelofibrosis is important but not destructive (Figure 13). Second, presence of dystrophic megakaryocytes with a scant, poorly defined cytoplasm and an elongated hyperchromatic nucleus along with massive myelofibrosis with focal deposition of coarse collagen fibers (Figure 14).[52] According to some authors the presence of a moderate number of blasts (10 to 20%) in bone marrow is not inconsistent with the diagnosis.[52] In general, the clinical course is rapidly progressive and the survival short,[51,53] except when myelofibrosis is associated with RA or RAS subtypes.[54] In spite of this poor prognosis, anecdotal cases of patients achieving a complete remission with prednisolone have been reported.[55] Myeloproliferative syndromes in acute phase and some *de novo* acute leukemias, particularly M7, may pose important problems of differential diagnosis with this form of MDS.[52] They can be distinguished from agnogenic myeloid metaplasia by the absence of splenomegaly, teardrop-shaped red blood cells and leukoerythroblastosis, and from acute megakaryoblastic leukemia by the absence or small percentages of blasts of megakaryocytic origin.[5]

MDS with abnormal chromatin clumping in granulocytes

This clinical picture was first reported in 1970.[56] Recently, more detailed descriptions have been made.[57–59] It occurs in elderly patients who presented in most cases with anemia and thrombocytopenia. The leukocyte count at presentation may be low, normal or sometimes elevated; it may increase during the evolution of the disease. The most striking anomaly is the presence of a highly condensed chromatin in the mature forms of the granulocytic series, associated with an hyposegmentation of the nucleus (Figure 15). The chromatin is clumped in large blocks separated by clear zones giving an aspect of *nuclear fragmentation*. In the peripheral blood, immature granulocytic precursors are often present but blast cells are rare or absent. There is no excess of monocytes, any basophilia or eosinophilia. A moderate dyserythropoiesis and dysmegakaryocytopoiesis are common. Cytogenetic studies display no Philadelphia chromosome and no abnormality of the 17p. Chromosomal abnormalities have been reported, mainly deletions or duplications.[57-59] A number of these patients present with infections (e.g., pneumonia) and hemorrhage, which are frequent causes of death. In spite of the low proportion of bone marrow blasts, the disease has an aggressive course and the life-expectancy is short.[59]

Primary MDS in children

MDS are uncommon in childhood. In two population-based studies, the incidence ranged from 0.53 to 3.4/1,000,000 children.[60,61] Major differences between childhood MDS and adulthood MDS exist with respect to the distribution of FAB subgroups, cytogenetic findings, rate of progression and survival.[62] In the series of Tuncer *et al*. all patients could be classified according to the FAB criteria.[63] Upon comparing this series with

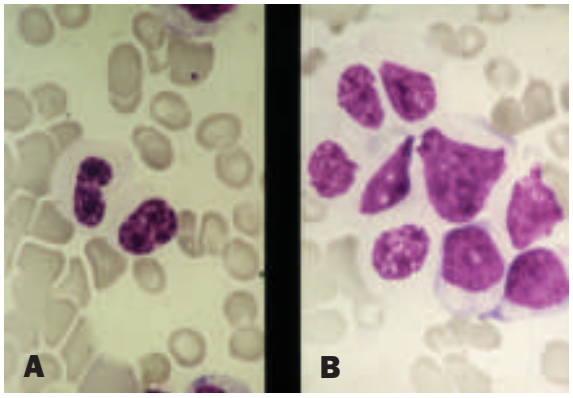

Figure 13. A: peripheral blood. Polymorphonuclears with abnormal chromatin clumping associated with hyposegmentation and degranulation. B: bone marrow. Abnormal chromatin clumping in the mature forms of the granulocytic series.

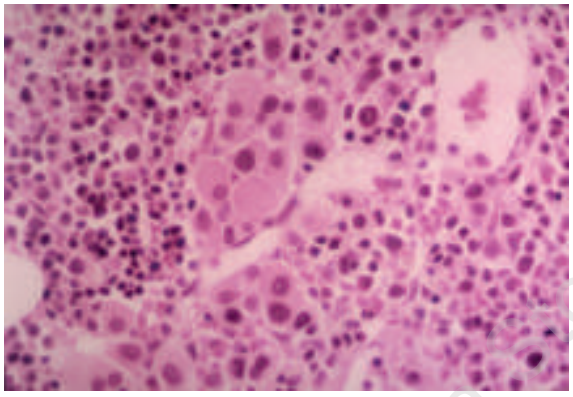

Figure 14. Bone marrow biopsy. Myelodysplastic syndrome with myelofibrosis: hypercellular marrow with small, hypolobulated megakaryocytes; presence of erythroblasts and some mature granulocytic cells.

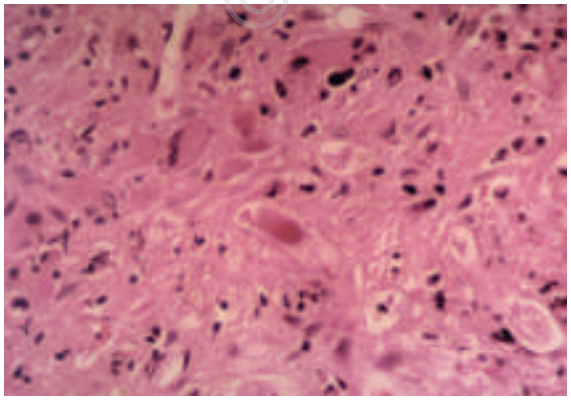

Figure 15. Bone marrow biopsy. Myelodysplastic syndrome with myelofibrosis: fibrotic stroma in which megakaryocytes are dystrophic with a poorly defined cytoplasm and elongated hyperchromatic nucleus.

adult cases, RAEB and RAEB-t were more frequently observed among children, while no RAS cases were found. Nevertheless, a very few cases of RAS in children have been reported.[64] The most common chromosome involved was number 7.[62,65] The overall median survival was short (5.5-9.9 months)[63,66] and there was a high rate of leukemic transformation; intensive treatment as used for *de novo* AML should be used.[66,68]

Passmore *et al*. have proposed to modify the FAB criteria by incorporating additional diagnostic features such as fetal hemoglobin level (HbF) and cytogenetics.[65] In a recent study from the St. Jude Children's Hospital the authors found 8/49 cases of pediatric MDS (< 30% of marrow blasts) with karyotypes associated with *de novo* AML: four with t(8;21), and one each inv(16), t(11;17), t(9;11) and i(1). All these 8 cases had less prominent myelodysplastic features and achieved a higher complete remission rate than the remaining 41 patients. These observations led to the authors to conclude that the 30% blast threshold is not useful to separate AML from MDS, and that genetic data should be included in the diagnosis and treatment decisions.[69]

Juvenile chronic myelomonocytic leukemia (JCML) is a disorder of the monocyte-macrophage cell lineage mainly affecting boys younger than 4 years of age. It is considered a distinct entity because of its characteristic combination of symptoms: hepatosplenomegaly, generalized lymph node enlargement, and facial rash together with the presence of thrombocytopenia, leukocytosis with increase of monocytes, nucleated red blood cells in peripheral blood, elevated HbF and hypergammaglobulinemia.[70,71] The *International Myelomonocytic Leukemia Working Group* defined a set of minimal criteria for the diagnosis and also suggested a new name for the disease, juvenile myelomonocytic leukemia (JMML) syndrome (Table 4).[71]

Secondary MDS

Cases of MDS related to chemotherapy and/or radiotherapy are increasingly being recognized as one of the most feared long-term complications of cancer therapy. These disorders are usually known as secondary MDS, therapy-related myelodysplastic syndromes (t-MDS) or cytotoxic MDS. The agents most frequently involved in the development of secondary MDS include alkylating agents, epipodophyllotoxins, and anthracyclines (Table 5).[72,73] Some cases of MDS and AML have been reported after treatment for solid tumors of childhood and, more recently, after treatment with mitoxantrone for breast cancer have been reported.[74,75]

MDS/AML after intensive chemotherapy and/or radiotherapy for Hodgkin's disease is the most studied malignancy with a percentage of relative risk ranging from 2.2 to 3.3 at 15 years.[76,77] In addition, some cases of MDS following high-dose chemotherapy and autologous stem cell transplantation for lymphoid malignancies have been described.[78] In contrast,

Table 4. Minimal criteria for the diagnosis of a juvenile myelomonocytic leukemia (JMML) syndrome.[71]

- WBC count > 13×10^9/L
- Absolute monocyte count > 1×10^9/L
- Presence of immature myeloid precursors (myelocytes, promyelocytes and myeloblasts) in the peripheral blood
- < 30% blasts in the bone marrow
- Exclusion of translocation t(9;22)(q34;q21) or BCR/ABL rearrangement

Table 5. Risk factors for t-MDS/AML.

Agent	*Leukemia risk increased*
Alkylating	Increasing cycles of MOPP or MOPP-like regimens Mechlorethamine rather than procarbazine
DNA topoisomerase II inhibitor	Cumulative dosis
Radiation	Radiation dose to active bone marrow Dose rate Percentage of marrow exposed

Table 6. Characteristics of secondary AML according to the implicated agent.

Alkylating	*DNA topoisomerase II inhibitor*
Highest risk in the 5-10 year follow-up period	Shorter induction period (2-3 years following treatment)
Often preceded by MDS (50% of AML cases)	Generally lacks preceding phase of myelodysplasia
Most commonly M1-M2 FAB subtypes	M4 or M5 according to the FAB criteria
Karyotype abnormalities: –7, 5q–, –5	Balanced translocations involving 11q23, 21q22
Resistant to antileukemic treatment	A somewhat better prognosis

MDS rarely appears after allogeneic transplantation which suggests that MDS develops from cells accumulating mutations because of the subablative administration of chemotherapy.[72]

The FAB classification is not useful to classify the majority of secondary MDS. This is due to the fact that although the percentage of blasts in bone marrow is usually less than 5%, many immature dysplastic erythroid, megakaryocytic and monocytic forms are present, with a high incidence of tri-lineage involvement.[79] In a multi-institutional Italian study the morphology of MDS occurring in Hodgkin's disease was evaluated: 37% of cases could not have been classified according to the FAB criteria.[80] In peripheral blood, macrocytosis with oval macrocytes and nucleated red blood cells, as well as the presence of hypogranulated neutrophils and pseudo-Pelger-Huët cells may be seen. In 20 to 50% of the cases the marrow is typically hypocellular with increased fibrosis.[72]

The majority of these patients with secondary MDS (90%) have an abnormal clone in cytogenetic analysis, with the most common abnormality being the loss of either part or all of chromosomes 5 and/or 7 (–7, 5q–, –5, in order of frequency).[72,73] These chromosome changes are different from the translocations frequently associated with *de novo* leukemias. Nonetheless, t-MDS/AML associated to high doses of epipodophyllotoxin presents a balanced chromosomal translocation including 11q23 or 21q22.[82] The behavior of this t-MDS/AML is very similar to that of patients with *de novo* AML with the same translocation (Table 6).[72,73]

Secondary MDS constitute an inexorable, rapidly progressing disorder with a short survival.[83,84] Michels *et al*. have suggested three stages of therapy-related panmyelosis: 1) pancytopenia with minor myelodysplastic features; 2) MDS; and 3) AML. MDS or AML may arise as a secondary disorder independently of the type of preceding malignancy or treatment, thus emphasizing the biological similarities between secondary MDS and AML.[83]

Cytogenetics of primary MDS

In primary MDS the discovery of non-random chromosomal aberrations has been extremely helpful to identify the malignant clone and also to characterize distinct clinical-pathological entities in which cytogenetic findings correlate with morphological features and/or with the clinical course of the disorder. Recently, integration of classical cytogenetics with DNA technology, by the development of fluorescent *in situ* hybridization (FISH), has been shown to further enrich the understanding of the biology of myelodysplastic disorders.[85] Some attempts have been made to determine the lineage affiliation of bone marrow and peripheral blood cells bearing the typical clonal aberration in MDS.[86]

In this short review chromosome changes of primary MDS will be discussed with distinction between changes frequent and/or specific for MDS, and changes occurring in MDS and also in AML or in MPD. Aberrations are summarized in Table 7 and Table 8.

Chromosomal changes typical of MDS

Del(5q) and the 5q- syndrome

Because the deletion of the long arm of chromosome 5 is a common finding in MDS, confusion occurs

Table 7. MDS changes.

Structural changes	*Typical hematological features*
5q-	RA, monolobulated megakaryocytes, macrocytosis, normal or high platelets
t(5;12)(q33;p13)	CMML
t(..;12)(..;p13)	eosinophilia, monocytosis
del(20)(q)	dyserythropoiesis
del(11)(q)	ringed sideroblasts
del(17)(p)	dysgranulopoiesis, pseudo Pelger-Huët
iso(X)(q13)	ringed sideroblasts
Numerical changes	
Monosomy 7	JCML, familial MDS, Fanconi anemia, t-MDS
–Y	
Trisomy 6	aplasia, dyserythropoiesis
Numerical/structural changes	
t(Y;1)(q12;q12)	
t(1;15)(p11;p11)	
t(1;16)(q11;q11)	

Table 8.

Structural changes	*Gene involvement*
AML/MDS changes	
t(6;9)(p23;q34)	DEK; CAN
t(3;5)(q25.1;q34)	MLF1; NPM
inv(3)(q21q26)	EVI1, ribophorin complex
t(1;3)(p36;q21)	–
t(3;21)(q26;q22)	AML1;EVI1; MDS1
del(9)(q)	–
Numerical changes	
trisomy 11	MLL/ALL1/HTRX tandem duplication
trisomy 4	–
trisomy 13	–
MDS/MPD changes	
i(17q)	–
trisomy 14/i(14q)	–
del(13q)	
t(6;9)(p23;q34)	DEK; CAN
trisomy 8	–
del(17)(p)	P53
del(20)(q)	–
AML changes in MDS	
t(8;21)(q22;q22)	ETO; AML1
inv(16)(p13q22)	MYH11; CBFB
t(9;22)(q34;q11)	ABL; MBCR/mBCR

in the distinction of the *5q- syndrome* from cases of MDS associated with del(5q).[39] Initially described by Van den Berghe *et al.*, the so-called 5q- syndrome is the strongest cytogenetic-pathological association in MDS.[87] Cytogenetically the 5q- anomaly occurs as the sole karyotypic change. This special syndrome is discussed elsewhere in this review.

This 5q- syndrome is observed in only about one third of the MDS with del(5q). 5q- anomaly in MDS is not limited to the 5q- syndrome as it is also seen in MDS subgroups others than RA, namely RAEB and RAEB-t. In such cases, however, it is usually associated with other karyotypic aberrations, as in acute myeloid leukemia.[88]

Analysis of a large number of MDS with del 5q has shown that the deletion is generally interstitial. The extent of the deletion is variable. However, the distal breakpoint is in 5q33 in 70% of the cases, and the proximal breakpoint in q13 and q15 in 50% and 20% of the cases, respectively.[89] The type of deletion is often correlated with clinical features. For example, the proximal breakpoint is closer to the centromere in elderly patients whereas the distal breakpoint is independent of age; del5(q13q33), the most common type of deletion (40% of the cases), is predominant in females, is generally the only chromosomal abnormality, shares clinical and hematological features with the 5q syndrome, and portrays a relatively good prognosis.[89] Precise analysis of chromosomal breakpoints of 93 MDS with del 5q showed that 91 cases lacked band 5q31, which is therefore the most common deleted region.[89] This region does not include the genes located on 5q that code for growth factors or their receptors, including GM-CSF, M-CSF, interleukins 3, 4 and 5. Extensive work has been performed to identify one or several tumor suppressor gene(s) in this deleted region.[90-92] Two genes (i.e., EGR 1 and IRF 1) and a locus (i.e., D_5S_{89}) are possible candidates, although none of them appears to be involved in all cases of MDS with del 5q.

Such single gene studies, however, demonstrated the existence of molecular heterogeneity among cases with a 5q– chromosome. A deletion mapping approach using chromosome walking to delimit the smallest deleted region is in progress. [93]

t(5;12)(q33;p13) and other t(...;12)(...;p13)

A t(5;12)(q33;p13) is a balanced translocation first described in chronic myelomonocytic leukemia by Srivastava *et al.*,[94] although the same abnormality can be observed in other MDS types.[95,96] Eosinophilia and monocytosis are common in such MDS, independently of the FAB subgroup. ETV6-TEL gene at 12p13 fuses with the receptor for platelet derived growth factor beta (PDGFBR) at 5q33. The product of the fusion gene is thought to induce malignant transformation through interference with RAS gene signaling. Variant chromosomal translocations involving ETV6 in MDS with eosinophilia and monocytosis have also been

found. Chromosome 3q26, 6p21, and 10q24 have been identified as partners of ETV6 translocations in MDS.[97-100] So far, the molecular counterpart has been only characterized at 3q26 in which MDS/EVI1 gene undergoes fusion with ETV6.[101]

Del(20)(q)

An interstitial deletion of the long arm of chromosome 20, as isolated karyotypic change, is common to MDS and myeloproliferative disorders, especially polycythemia vera.[102-103] This type of distribution among hematological malignancies is interesting since the erythroid compartment, primarily involved in polycythemia, also presents the most relevant dysplastic features in MDS with 20q–.[103] Indeed this anomaly is found in bone marrow precursors generating not only myeloid elements but also a sub-population of B lymphocytes.[104] The aberration seems to influence the kinetics of bone marrow cells with impaired dismission into circulating blood of immature granulocytes which bear the anomaly.[105] Cytogenetically, interstitial or terminal deletions of variable size have been described.[106] Molecular investigations, however, agree in defining all deletions as interstitial with the crucial region being between $D_{20}S_{174}$ and $D_{20}S_{17}$ loci, where several candidate tumor suppressor genes have been localized.[107] The prognostic significance of 20q deletion is controversial. It is possibly relevant whether the anomaly is isolated or associated with multiple karyotypic changes.[108] In the recently published *International MDS Risk Analysis Workshop* a relatively good outcome was found similarly to the 5q- anomaly.[109]

Del(11)(q) and idic(X)(q13)

These structural chromosomal changes have been reported as typical of RAS and other MDS types in which ringed sideroblasts are present in the bone marrow.[110,111] These two abnormalities are not associated in RAS suggesting the existence of two independent mechanisms in the pathogenesis of this disorder. Interestingly, a recent hypothesis on the mitochondrial origin of RAS emphasized the occurrence of chromosome changes as a late event in the development of this peculiar type of MDS.[112]

Deletions on the long arm of chromosome 11 always involve band q14 where the gene for the H sub-unit of ferritin is located.[113] A number of genes potentially involved in leukemogenesis have been located at Xq13.[114]

Monosomy 7

This is a very frequent anomaly in secondary disorders after therapy with alkylating agents or occupational exposure to chemical mutagens and is better detected by FISH.[115,116] Primary MDS is mainly found among children, which are frequently affected by congenital disorders, such as familial myelodysplasia, Fanconi anemia, and type I neurofibromatosis.[117] Whether the presence of monosomy 7 reflects a common pathogenetic pathway is unknown. The poor prognostic significance of this abnormality has been largely proved by either the high incidence of progression to acute leukemia or the high incidence of bacterial infections due to neutrophilic defects in chemotaxis.[118] In myelodysplastic syndromes the bone marrow is frequently hypoplastic and cases of aplastic anemia with monosomy 7 have been also described.[44] Parental imprinting of the missing chromosome 7 seems unlikely.[119] In JCML a model of development of monosomy 7 preceded by RAS or NF1 gene mutations has been proposed.[120]

Trisomy 8

This is the most common single chromosome abnormality in *de novo* AML. In primary MDS, the incidence of trisomy 8, either alone or associated with other abnormalities, ranges between 10% to 15%.[5] The presence of an extra chromosome 8 has been associated with M4 and M5 subtypes and with MDS with a monocytic component.[121] The median survival of MDS patients with trisomy 8 ranges from 25 to 57 months.[122,123]

–Y

The significance of the loss of chromosome Y in malignancies is intriguing, since it has been correlated with aging in normal individuals.[124] It emerged as non-random change in chronic myelomonocytic leukemia.[125] In acute leukemia loss of Y is usually an additional aberration to a typical rearrangement, such as t(8;21).[106] There are also cases of acute leukemia in which a clone with an isolated –Y disappears when complete remission is achieved emerging again at relapse. Interestingly, at the *Sixth International Workshop on Chromosomes in Leukemia* progression to acute leukemia was never found in MDS with –Y.[125] A recent report in this journal suggest that MDS patients with loss of chromosome Y may dysplay a higher survival rate.[126]

Trisomy 6

This numerical aberration has been shown to be helpful in the differential diagnosis between aplastic anemia and myelodysplastic syndromes with bone marrow hypoplasia.[44] The involvement of myeloid and erythroid dysplastic elements has been clearly shown combining FISH with morphology.[127] A case of trisomy 6, classified as aplastic anemia in which trisomy 6 disappeared at time of evolution to acute leukemia when monosomy 7 was evidenced, has been reported.[128] According to the information available on eight cases published, trisomy 6 is not associated with an aggressive clinical course.[127]

Translocations involving 1q

The following translocations involving 1q chromosome have been found in primary MDS: t(Y;1)(q12;q12); t(1;15)(p11;p11); t(1;16) (q11;q11).[129-131]

These changes derive from a trisomic long arm of chromosome 1 (1q) which alternatively rearranges with chromosome Yq12, 15p11, or 16q11. Thus, cytogenetically, they may be considered as either numerical changes (because of partial trisomy) or structural changes (because of juxtaposition of the heterochromatic region of chromosome #1 with distinct chromosome bands of chromosome Y, 15, 16). There is no correlation with FAB subgroups of MDS. Total and partial trisomy of 1q are well established changes in both myeloproliferative disorders and also some acute lymphoid leukemias, in which they are supposed to confer a proliferative advantage to the affected cells.

Chromosomal changes common to MDS and AML

This is a group of structural and numerical rearrangements which can be found in both MDS and AML (Table 2). Changes like t(6;9) translocation may also be associated with chronic myeloproliferative disorders.[132] This justifies the classification of the accompanying disorders within a *chromosomal syndrome* including different clinico-hematological manifestations.[133,134] It is tempting to speculate that the chromosomal anomaly interferes with a general mechanism common to different pathogenetic pathways. In some of these changes the molecular counterpart has been characterized and no differences have been found between MDS and AML. Since MDS are thought to originate at the level of an early progenitor, at least of a multipotent myeloid stem cell, these aberrations have been associated with the concept of stem cell disorders. The numerical changes reported in Table 2 are rare in MDS. FISH has documented trisomy 11 in hematopoietic lineage derived from a common myeloid precursor.[135] On its turn, trisomy 4 has been sporadically observed in blast cells expressing lymphoid antigens.[136] Finally, FISH has documented trisomy 13 in CD34 positive precursors.[137]

Chromosomal changes common to MDS and MDP

These anomalies are listed in Table 2. All but t(6;9) have also been found in Ph-positive chronic myeloid leukemia. This group of changes is interesting since there are disorders that are defined as borderline between MDS and MPD, on morphological grounds. Trisomy 14 and isochromosome for #14 have been described in such borderline disorders.[138] Trisomy 14 and i(14q) are possibly equivalent in terms of biological significance leading to an unbalanced karyotype with gain of the same genomic material.

Chromosomal changes of AML in MDS

The typical chromosomal changes in AML, t(8;21), inv(16), and t(9;22), have been well characterized at the cytogenetic and molecular level in MDS. Although sporadic, these observations are interesting because they suggest that blasts bearing such anomalies may keep some differentiating properties. Also, the presence of such aberrations might be helpful to make treatment decisions.

Specific chromosomal syndromes in MDS

Although no striking morphological-genetic molecules entity – such as acute promyelocytic leukemia – has been defined so far within MDSs, some cytogenetic-clinical correlation have been found.

The 5q- syndrome

The so-called 5q- syndrome is the strongest cytogenetic-pathological association in MDS.[87] Morphological stigmata, such as hypolobulated megakaryocytes, anemia with macrocytosis, erythroblastopenia, and normal or increased platelet count are always present.[139,140] In this syndrome, 5q- is the sole karyotypic change. In cases of isolated del 5q, normal mitoses almost always persist in association with mitoses with del5q, whereas this is less often the case in MDS with del5q and other abnormalities.[90,139] Deletion is always interstitial, but variations are seen of proximal and terminal breakpoints, and, consequently, of the size of the DNA segment which goes lost.[141] Critical breakpoints may also be involved in paracentric inversions.[142,143] In the typical 5q- syndrome, however, the band 5q31 is constantly lost.[90] In this region, indeed, major efforts have been made from different groups to identify the gene(s) involved in the pathogenesis of the disorder. Interestingly, within the 5q- deleted region, there is a clustering of an impressive number of regulatory genes for the hematopoietic system, including growth factors, growth factor receptors, and oncogenes.[90] Attention has been focused on mutations and deletions of c-FMS, the receptor for the M-CSF; on deletions of IRF1, an interferon regulating factor; on deletions of a tyrosine kinase gene FER and of a zinc finger gene EGR1.[88]

The *5q- syndrome* is generally associated with a high RBC transfusion requirement and a low risk of progression to AML (about 10%).[90,139,140] Anemia, in the *5q- syndrome*, generally results from quantitative erythropoietic aplasia, and is reflected by absolute erythroblastopenia on marrow smears (rather than erythroblastosis, observed in most MDS). The 5q- syndrome is (like RARS) one of the subgroups of MDS where the major risk, during evolution, is iron overload. In the absence of any specific treatment, all efforts should focus on iron chelation, mainly by long term subcutaneous desferrioxamine.

17p deletion in MDS

In about 5% of MDS, unbalanced translocations between 17p and another chromosome (predominantly chromosome 5 or 7) monosomy 17 or less often i(17q), all resulting in 17p deletion, have been found.[144] These cases were often therapy related and all had an excess of marrow blasts. The most frequent unbalanced translocation leading to del 17p was t(5;17)(p11;p11), followed by t(7;17) (p11;p11), and

Table 9. Future trends.

a) Refractory cytopenia with multilineage dysplasia (RCMD) should be included into the FAB classification.[38]

b) RAS may be segregated into two types: "Pure" sideroblastic anemia (PSA) and refractory anemia with ring sideroblasts (RARS).[25]

c) CMML myeloproliferative type could be included into myeloproliferative disorders but not only on the basis of the WBC count.[34,35]

d) The presence of Auer rods does not imply a worse prognosis.[29]

e) Some authors propose to consider as acute myeloid leukemia (AML) younger patients with less than 30% of blasts cells in peripheral blood or bone marrow but with minimal myelodysplasia and karyotype findings typical of *de novo* AML.[69]

f) The recognition of other clinical-morphological subtypes: MDS with myelofibrosis, primary MDS in children and therapy-related MDS.[1,4]

g) t-MDS should be classified according to the agent implicated and karyotype.[77]

h) Chromosomal abnormalities would be added to the diagnosis and classification of MDS.[69]

i) Several cytogenetic abnormalities such as deletion 5q and deletion 17p, associated to specific morphological features, might be recognized as separated MDS syndromes.[139,144]

RA: refractory anemia; CMML: chronic myelomonocytic leukemia.

translocations between 17p11-p13 and others chromosomes 12, 21, 15, 22.[145] Almost all patients had at least 2 other cytogenetic rearrangements. In more than 75% of the cases, a particular type of dysgranulopoiesis, combining pseudo Pelger-Huët hypolobulation of the nucleus and small vacuoles in neutrophils was seen. Combination of these two abnormal features was almost never found in MDS without 17p deletion. The same typical dysgranulopoïesis has also been described in CML in blast crisis, where it is strongly correlated with the presence of i(17q), a cytogenetic rearrangement that also results in del 17p.[146] Isochromosome 17q found in MDS is also associated with this type of dysgranulopoiesis. In 70% of the patients with 17p deletion, a point mutation of the p53 gene, located in 17p13 was found. By contrast, a p53 mutation was found in only 3% of MDS without 17p deletion in our experience. Therefore, in most MDS with del17p, both p53 alleles were inactivated in neoplastic cells (one p53 allele being lost due to 17p deletion, and the other being inactivated by point mutation).

3q rearrangements

Approximately 2% of MDS have rearrangements in 3q, consisting of inv(3)(q21q26), t(3;5)(q25q34), t(3;3)(q21;q26) or other less frequent abnormalities. These patients almost always present themselves with an excess of marrow blasts, and 30 to 50% of the cases are therapy related.[147,148] Dysmegakaryopoiesis mainly consisting of micromegakaryocytes, is present in 90% of the cases and, contrary to other MDS with excess of marrow blasts, platelet counts are normal (50% of the cases) or even increased (20% of the cases). Response to chemotherapy is generally poor and survival short.

The EVI 1 gene located in 3q26 encodes a zinc finger DNA binding protein originally described as a transforming gene associated with a common ecotropic viral insertion site in myeloid leukemias. Chromosomal breakpoints on 3q26 in t(3;3)(q21;q26) occur approximately 330 Kb upstream of the EVI 1 gene, and those of inv(3)(q21q26) occur downstream of the EVI 1 gene. In both situations, transcriptional activation of EVI 1 gene is observed, and it has been hypothesized that this inappropriate inactivation could interfere with normal differentiation. In particular, EVI 1 can block the transcriptional activity of GATA-1, a factor required for normal erythroid differentiation, in cell lines.[149]

It has also been shown that breakpoints in 3q21, both in t(3;3) and inv(3), are clustered over a region 50 Kb downstream of the ribophorin I gene. Inv(3) and t(3;3) could result in the transcriptional activation of the EVI 1 gene by enhancing the elements associated with the ribophorin I gene.[150] However, the EVI 1 gene is also activated in about 30% of MDS without 3q rearrangements, almost exclusively in RAEB and RAEB-T; the mechanism of activation of the gene in these cases is unknown.[151]

Finally, although the thrombopoietin gene is located on 3q26, this gene is distant from EVI 1 gene by at least 600 Kb, and it is not rearranged in the translocation or inversion of 3q.[152]

t(3;21) translocation

Several cases of MDS with t(3;21)(q26;q22), generally occurring after treatment with alkylating agents or epipodophyllotoxins or in rare cases after exposure to organic solvents, have been reported.[153,154] These cases had no specific hematological findings, but were associated to an excess of marrow blasts and, contrary to MDS with t(3;3) or inv(3), with thrombocytopenia.

This translocation has also been observed in CML.[153] It has been demonstrated that it leads to a fusion between AML 1 gene[155] on 21q22 and one of the following contiguous genes in 3q26 : MDS1, EAP or less often EVI1.[153,156] The AML 1/EVI 1 fusion protein has shown transforming activity after transfection into fibroblasts.[157]

In conclusion, description of new cytogenetic-morphological correlations in MDS, and, further genetic analysis of already described *specific* chromosomal syndromes in MDS should eventually help, as in the case of AML, to discover genes implicated in the pathogenesis of MDS.[158] Hopefully, the better description of these MDS *syndromes* will lead to specific forms of treatment, as in the paradigm constituted by acute promyelocytic leukemia and retinoic acid.[159,160]

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