VOL 19, NO 1 FEBRUARY 1992

Seminars in

Myelodysplastic Syndromes

Donald C. Doll, MD, and Alan F. List, MD, *Guest Editors*

Contributors

Donald C. Doll • Alan F. List • Jean E. Goasguen
John M. Bennett • Allan Jacobs • Peter C. Nowell
Peter L. Greenberg • Ellis G. Levine • Clara D. Bloomfield
Bruce D. Cheson • Masahiro Kizaki • H. Phillip Koeffler

Seminars in Oncology

Myelodysplastic Syndromes

VOL 19, NO 1 **FEBRUARY 1992**

Table of Contents

Classification and Morphologic Features of the Myelodysplastic Syndromes

Jean E. Goasguen and John M. Bennett

PATIENTS WITH variable degrees of unexplained cytopenia(s), usually associated with a hypercellular marrow, have been classified as primary acquired myelodysplastic syndromes (MDS). In the past MDS enjoyed a diverse terminology, including "preleukemic acute leukemia,"[1] "smoldering acute leukemia,"[2] "refractory anemia,"[3] "refractory anemia with excess of myeloblasts,"[4] "smoldering myeloid leukemic states,"[1] and "dyshematopoiesis."[6] Those who use the term "preleukemic" do so primarily in a restrictive sense, because theoretically all patients so described have acute leukemia and can be traced historically to have a chronic evolving bone marrow disorder that terminates in "overt" acute myeloid leukemia (AML). We now know that approximately 15% to 20% of MDS evolve to AML. The majority of these patients are older than age 50 years and have evidence of morphologic abnormalities of the myeloid lineage similar to those observed in AML, but with less than 30% blasts in the marrow aspirate. The French-American-British (FAB) Cooperative Group attempted to characterize these entities into five subgroups, based on the recognition of dysmorphic features common to all groups, and other criteria distinguishing them. Since this description' in 1976, revised in 1982[8] and in 1985,[9] several cases of MDS in young patients as well as in children have been reported and will also be discussed.

Dacie et al,[5] based on the apparent double red cell population observed on peripheral blood smears of refractory sideroblastic anemia (RAS) patients, were the first to suspect the clonality of the MDS. This hypothesis was verified by studying the glucose-6-phosphate-dehydrogenase (G6PD) enzyme system in patients with MDS. Furthermore, cytogenetic studies showed involvement of multipotent stem cells in MDS patients." Using restriction fragment length polymorphisms of the X chromosome genes hypoxanthine phosphoribosyl transferase and phosphoglycerate kinase, Janssen and associates" demonstrated that MDS arise from a multipotent hematopoietic stem cell with the potential for both myeloid and lymphoid differentiation. This finding may explain the coexistence of lymphoid or plasmacytic neoplasms with MDS reported in the literature. Because a multipotent stem cell is involved in MDS, abnormalities of all lineages may occur. The diagnosis of MDS is based on dyspoiesis of trilineage cells in the bone marrow.

DYSERYTHROPOIESIS

Qualitative dyserythropoiesis (Figs 1 and 2) may include ringed sideroblasts, multinuclear fragments, bizarre nuclear shapes, internuclear bridging, mitosis, abnormal dense chromatin or fine chromatin with asynchronous cytoplasm, and abnormal cytoplasmic features (intense basophilia, Howell-Jolly bodies, ghosted cytoplasm). Anisocytosis, poikilocytosis, nucleated red blood cells, and acanthocytes may be seen on examination of the peripheral blood smear.[11a]

It has been recognized for years that there are several types of iron granules in the cytoplasm of erythroid precursors.[12,13] These ferritin aggregates are seen in normal marrows in a variable percentage of normoblasts (usually less than 50%) and rarely exceed 4 granules/cell.[14] The occurrence of 5 or more granules is considered pathologic (Fig 3) and when these granules comprise more than one third of the nuclear rim, the term "ringed" sideroblast has been used.[15,16] Ringed or abnormal sideroblasts can be found in a variety of hematologic conditions as well as in MDS. The disruption of mitochondria and observed changes in heme synthesis are the result of ineffective erythropoiesis, pre-

From Université de Rennes, Laboratoire d'Hematologi et d'Immunoligie Hopital SUD, Rennes, France; and University of Rochester School of Medicine and Dentistry, Department of Medicine and the Cancer Center, Rochester, NY.

Color photomicrographs were made possible by an Educational Grant to Donald C. Doll by the Burroughs Wellcome Company.

Address reprint requests to Dr Jean E. Goasguen, Laboratoire d'Hématologie et d'Immunologie Hopital Sud, 16 Boulevard de Bulgarie Rennes 3500, France.

0093-7754/92/1901-0002$05.00/0

mature erythroid destruction, and refractory anemia.

Quantitative changes may include the presence of an increased percentage of ringed sideroblasts (usually > 15% of all erythroid nucleated cells) and erythroid precursors comprising between 5% and 50% of bone marrow cells. If erythroid precursors account for greater than 50% of bone marrow cells and there are more than 30% blasts, then the diagnosis is erythroleukemia.

In the FAB proposals,' refractory anemia (RA) was differentiated from refractory anemia with ringed sideroblasts (RARS) by the presence of more than "15% ringed sideroblasts of all nucleated cells in the marrow." Subsequent to this publication considerable confusion arose. Galton[16] stated that the "main criterion was 15% of bone marrow erythroblasts." But as noted by Juneja et al,[17] the majority of cases of RARS had greater than 20% ringed sideroblasts (median, 40%). In the Cazzola" series all patients had ring sideroblasts greater than 15% of untreated red cells. With appropriate nuclear counter stains for erythroid precursors, it seems reasonable that 15% ringed sideroblasts of erythroid cells might be the lower limit to include such patients as **RARS.**

DYSGRANULOPOIESIS

Abnormalities of granulocytes are common in MDS and are present in both the peripheral blood and bone marrow. The most common abnormalities are hypogranulation (Fig 4) that may be associated with a negative peroxidase reaction, and hyposegmentation of the polymorphonuclear leukocytes with chromatin condensation (Pelger-Huet like anomaly) (Fig 1). In some cases granules may be absent and the polys are referred to as agranular. **A** classification of this abnormality has been proposed by Hast et al[19] for evaluation of dysgranulopoiesis in MDS. The defect in granulation may be seen only in myelocytes early in the course of disease. Occasionally, the chromatin appears clumped where blocks of chromatin are separated by a clear space, leading to an appearance of nuclear fragmentation associated with a loss of segmentation. Such clumped chromatin pattern has been associated with MDS and myeloproliferative disorders.[20-22]

In 1984, Langenhuijsen[23] described the presence of granulocytes with a nuclear hole (ring-shaped nuclei) in patients with myeloproliferative and myelodysplastic diseases. Van der Weide et al[24] observed ringed granulocytic nuclei in 32% of MDS cases. These cells probably represent a transitional stage to the band form (acquired Pelger-Huet formation) and are considered a sign of abnormal maturation.

In addition, so-called nuclear "sticks" can be noted, particularly in cases of secondary MDS or therapy related MDS. In the bone marrow persistent cytoplasmic basophilia of the rim of the cell may be evident as well as abundant azurophil granules or larger granules than usual. Moreover, the function of neutrophils may be affected in MDS patients. Phagocytic adhesion, chemotaxis, and microbicidal capacities may be impaired, but no correlation has been found between the presence and degree of hypogranulation and neutrophil function.[25,26]

DYSMEGAKARYOCYTOPOIESIS

Common abnormalities of megakaryocytes include micromegakaryocytes (Fig 5), multiple small nuclei separated by strands of nuclear material, and large mononuclear cells with dysmorphic nuclear features. To enhance the ability to recognize micromegakaryocytes the use of the CD41 monoclonal and antifactor VIII antibody*' may be helpful. The 5q- syndrome is frequently associated with an abnormality of megakaryocytes, which are usually small, with a single eccentric round nucleus. Dysmorphic features have been reported and classified by Jinnai et al[28] for the evaluation of dysmegakaryocytic features in MDS-associated AML. In addition, a recent study by Wong and Chan[29] recognized hypogranular megakaryocytes in 80% of MDS.

DYSMONOCYTOPOIESIS

Mature monocytes and their precursors can be identified in the bone marrow and peripheral blood film by use of esterase stains (usually the double esterase technique). This technique allows for an evaluation of the monocyte clonal proliferation and an estimate of the threshold of the monocyte population. It also permits one to recognize dysmorphic monocytic features (Fig **6)** which may be observed in the more mature

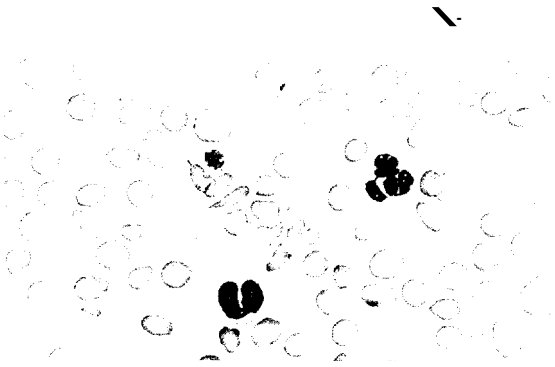

Fig 1. Anisocytosis and hypochromic red cells; agranular neutrophils with condensations of nuclear chromatin (pseudo-Pelger-Huet cells); giant platelets. Peripheral blood. May-Grunwald-Giemsa (MGG) stain.

Fig 2. Dyserythropoiesis with nuclear budding and internuclear bridging. Bone marrow, Wright-Giemsa stain.

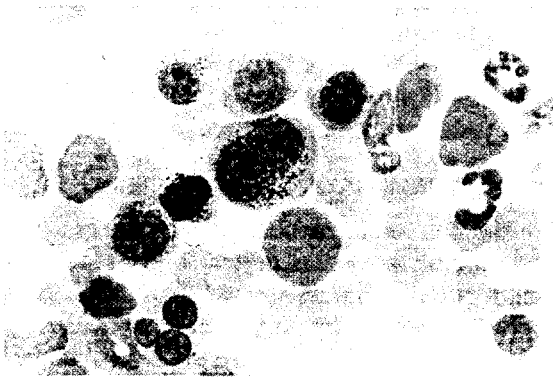

Fig 3. Many abnormal sideroblasts with multiple granules (ringed forms) in both immature and mature erythroblasts. Bone marrow, Prussian blue reaction.

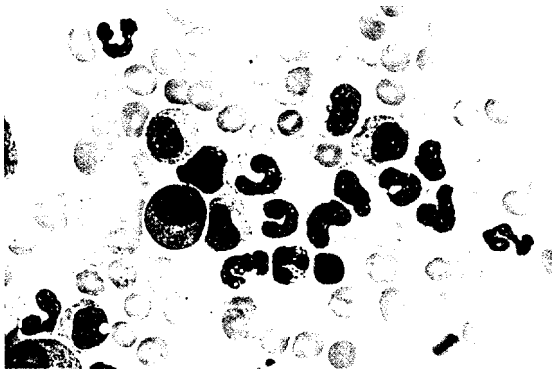

Fig 4. Hypo- and agranular myelocytes, metamyelocytes and neutrophils. FAB type: Refractory anemia (RA). Bone marrow, MGG stain.

cells but are frequently overlooked in the immature precursors. The monocytic population can also be demonstrated by monoclonal antibodies CD13 and CD14.

THE CYTO-IMMUNOLOGICAL DIAGNOSIS OF MDS

The diagnosis of MDS may be enhanced by the application of certain cytochemical and immunocytochemical techniques. The peroxidase or Sudan Black B reaction may confirm the myeloid origin of blast cells; nonspecific esterase or a double esterase reaction can identify early monocytic precursors and differentiate these cells from poorly granulated myelocytes. Double esterase stains[29] can also distinguish a population of early myeloid/monocytic cells (by the presence of both granulocytic and monocyte esterase) in marrows. Similar stained cells have been described in **FAB** M4 (acute myelomonocytic leukemia).

Immune marker analysis for myeloid and lymphoid cells may provide insight into lineage association of acute leukemias and has been described in previous publications.[31,32] In megakaryocytic dysplasia the abnormally small megakaryoblasts ("dwarf cells") may resemble lymphoid precursors ("L2" blasts). These cells can be recognized with immunocytochemistry on air dried smears with a CD41 antibody revealed by alkaline phosphatase anti alkaline phosphatase **(APAAP)** technique." Lymphoid blasts can be confirmed by a CD34 monoclonal antibody or by CD19 and CD10 antibodies.[33] Erythroid precursors may be diagnosed by a glycophorin **A** antibody and immature myeloid

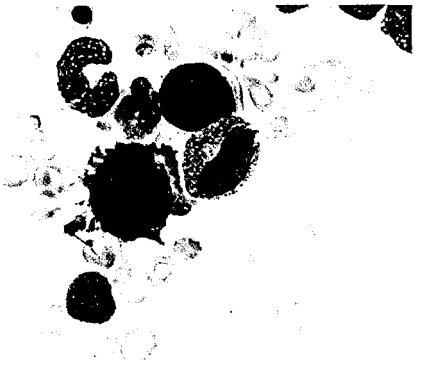

Fig 5. Mononuclear dysplastic megakaryocyte ("dwarf form"), hypogranular myelocytes, promyelocytes and basophilic erythroblast. Bone marrow, MGG stain.

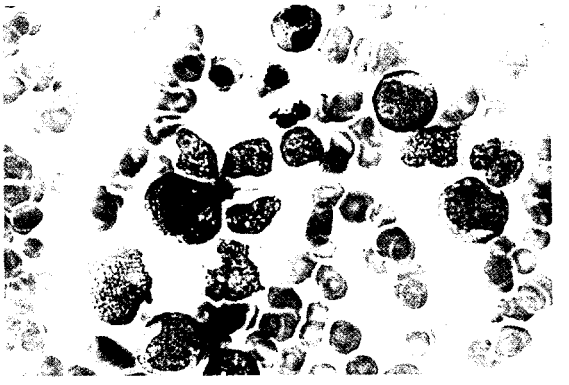

Fig 6. Hypogranular neutrophils, several blasts, dyserythropoiesis and monocytes. Bone marrow, MGG stain.

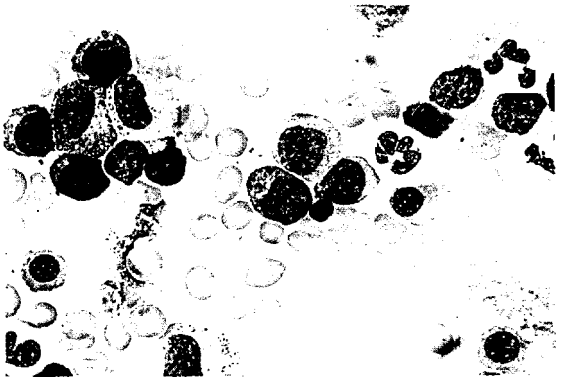

Fig 7. Type I, type II blasts (a few granules, less than 20) and blast with at least 20 granules ("typeII"). Note absence of golgi zone. Bone marrow, MGG stain.

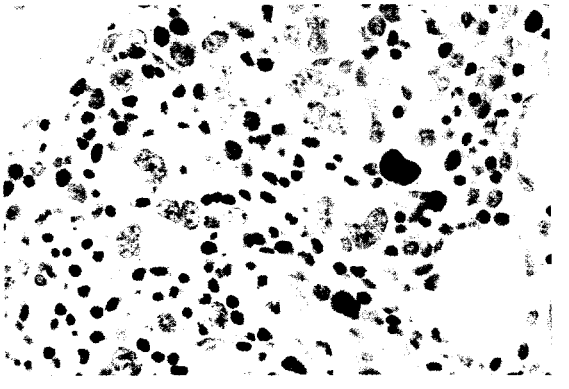

Fig 8. Hypercellular bone marrow with numerous dysplastic mononuclear and hyperlobated megakaryocytes, containing pale cytoplasm. Note: so-called "mummified cell." Hematoxylin and eosin stain.

progenitors may be quantified by using a CD13, CD14, and CD33 monoclonal antibody panel.[34,35] Because expression of CD13 and CD33 antigens on immature myeloid cells may be variable, some authors[35,36] recommend using a mature/immature myeloid ratio. Guyotat et al[36] used a CD34 antibody that was only positive in refractory anemia with excess blasts cases and was significantly associated with progression to leukemia and short survival. Moreover, the significance of CD34 positive cells in **AML** has recently been reported in 96 adult patients, demonstrating a lower complete remission rate after intensive cytoreductive therapy (59% *v* 87%).[34] The goal of such investigations has been to classify the lineage of blast cells, because the prognosis of such patients has been shown to correlate with the number of CD34 positive cells.

BLAST CELL CHARACTERISTICS IN MDS

The FAB classification of MDS established criteria for the definition of blast cells.[7-9] Type I blasts are defined by the absence of azurophil granules; type II blasts have identical features but contain "a few primary (azurophil) granules" (Fig 7). The FAB group did not define the upper limit of how many granules could be present. Potentially, this could result in ambiguity in distinguishing myeloblasts from promyelocytes and might explain the variability in the MDS subclasses reported in the literature.

The percentage of blasts in the bone marrow is the single most important prognostic factor in MDS, both in terms of overall survival as well as leukemic transformation. The **FAB** classification recognizes three groups of patients in terms

of percentage of blasts: cases with less than 5% blasts, cases with 5% to 20% blasts. and patients with 21% to 30% blasts. However, a study by Sanz et al[37] demonstrated a survival difference between patients having 5% to 10% blasts from those with 11% to 20% blasts. Moreover, it may be difficult differentiating promyelocytes and hypogranular myelocytes. In view of this, we recently introduced[38] another blast cell termed "blast type III," for myeloblasts with more than 20 azurophilic granules in the cytoplasm and not displaying a golgi zone (Fig 7). In a series of 18 patients with MDS,[38] we examined the prevalence of hypergranular myeloblasts (type III) and detailed the concordance of observers as well as the impact of counting these cells among agranular blasts (type I) and granular blasts (type II) on survival and leukemic progression. Our data suggest that these newly identified blast cells (type III) may be helpful in identifying a subset of patients with a poor prognosis.

BONE MARROW HISTOLOGY

A bone marrow biopsy is strongly recommended in the evaluation of MDS and provides an excellent appreciation of the cellularity (Fig 8). For example, in cases of hypocellularity associated with pancytopenia, patients with MDS might be confused with aplastic anemia, even if features of mild dysmyelopoiesis are observed. The following criteria may be useful in diagnosing hypocellular MDS[39]: abnormal localization of immature precursors (ALIP) located centrally in the medullary tissue instead of lining the endosteal surface; an increase of immature myeloid precursors; an island of erythroblastic precursors; and micromegakaryocytes and megakaryoblasts. which may be identified by the CD41 or factor VIII monoclonal antibody.

Myelofibrosis may be present in therapy-related MDS but is not a common feature of primary MDS.[40,41] Primary **MDS** may be associated with increased megakaryopoiesis, absence of organomegaly, and comparatively long patient survival. Such characteristics distinguish these cases from those previously described as acute myelodysplasia with myelofibrosis and malignant myelosclerosis."

CLASSIFICATION OF THE MYELODYSPLASTIC SYNDROMES

Refractor),Anemia

Characteristically, patients with RA have anemia, which is the hallmark of disease. The anemia is refractory with an absolute low reticulocyte count. may vary from mild to severe, and is not related to age. Granulocytopenia and/or thrombocytopenia may be minimal or absent. The bone marrow usually shows erythroid hyperplasia and dysmegakaryocytopoiesis may be absent. Agranular or hypogranular neutrophils may or may not be observed in the peripheral blood. Blast cells are usually not present in the peripheral smear (or very rarely, less than 1%) and by definition, are less than 5% in the bone marrow. Ringed sideroblasts are infrequent and are always less than 15% of erythroid marrow cells. RA accounts for approximately 17% of cases of MDS.

Refractory Anemia With Ringed Sideroblasts or Acquired Idiopathic Sideroblastic Anemia

There are similar features to RA except that there are greater than 15% ringed sideroblasts in the bone marrow. The blood cell volume is frequently greater than 100 fL and the bone marrow may reveal punctuated erythrocytes and erythroid precursors with an empty and lamellar cytoplasm. The marrow blast cells are always less than 5%. When ringed sideroblasts greater than 15% are associated with an excess of blasts (more than 5%), the syndrome is classified as refractory anemia with excess of blasts (RAEB) according to the FAB definition. In RAS (without blasts) leukemic evolution is rare, because the sideroblastic cell clone is relatively stable. When the disease progresses, the pathological cell clone increases in number and proportion, and ringed sideroblasts may represent as many as 80% of erythroid cells.

In a study of 94 patients with RARS, Gattermann et al[42] described sideroblastic anemia with abnormalities confined to dyserythropoiesis. and RARS with additional dysplastic features of granulopoiesis andior megakaryopoiesis. This study showed a striking difference in the risk of leukemic transformation between the two **popu**lations (5-year cumulative rate 1.9% v 48%) and overall survival (5-year survival 69% v 19%).

These results emphasize the differences between pure sideroblastic anemia and sideroblastic anemia associated with other dysplastic lineage features.

Lastly, one case of RARS evolving to chronic myelomonocytic leukemia (CMML) associated with inv(12) has recently been published[11] but the presence of dysgranulopoiesis was not noted.

Refractory Anemia With Excess of Blasts

RAEB is associated with conspicuous changes in granulocytes, which are hypo- or agranular, sometimes with abnormal chromatin or segmentation. Thrombocytopenia is common, but is usually mild. Occasional blasts may be present in the peripheral blood but are always less than 5%. The bone marrow is usually hypercellular with 5% to 20% blasts (type I and type II). In some cases type III blasts have been described[38] and may portend a worse prognosis. If included with type I and type II blasts they permit a change in the diagnosis in some cases. RAEB progresses more frequently to AML than RA and RARS. Moreover, the presence of abnormally localized immature myeloid precursors in the trephine biopsy has been described by Tricot et al[44,45] as an adverse prognostic factor.

Refractory Anemia With Excess of Blasts in Transformation

RAEB in transformation (RAEB-t) includes cases with the same dysmorphic features as RAEB but the percentage of blast cells is greater than 5% in the peripheral blood and/or is 21% to 30% in the bone marrow. When the percent of marrow blasts approaches 30% it may be difficult to differentiate RAEB-t from AML. In such cases, type III blasts should be considered, because their identification may change the diagnosis to AML.[38]

Weisdorf and coworkers[46] described five patients with the features of RAEB but with occasional Auer rods. The median survival was 14 months (range. 2 to 27 months) which did not differ significantly from RAEB as described by others. To recognize this entity the FAB group has included RAEB (5% to 20% of blasts) with Auer rods in the RAEB-t group. In younger patients (< 45 years) it is likely that this variant would rapidly evolve to overt AML.

As depicted in Tables 1 and 2 the median survival and leukemic transformation rate of MDS subclasses may vary. Differences evident among these results may be secondary to the identification of types of blasts and the number of patients.

However, three findings appear relevant: (1) survival is correlated with the presence of type I blasts in the marrow, as demonstrated by Sanz et al[37]; (2) the addition of type III blasts portends a worse prognosis[38]; and (3) the overall leukemic transformation rate for MDS is approximately 20%.[47] In patients with RAEB-t, the percent of leukemic transformation may vary from approximately 50% to 100%, however.

In the initial FAB proposals for MDS it was felt that the presence of 5% or more blasts in the peripheral blood film and a bone marrow that fulfilled criteria for MDS (less than 30% blasts) would warrant a diagnosis of RAEB-t. However. the observation that some patients presenting with greater than 30% of peripheral blood blasts and less than 30% marrow blasts evolved to AML within 2 months[11] suggests that an upper threshold of 20% to 30% marrow blasts would be reasonable to maintain for RAEB-t.

Chronic Myelomonocytic Leukemia

There continues to be controversy over the definition of CMML and the inclusion of this category among the MDS. As noted by Galton[16] some patients with chronic myelogenous leukemia (CML) may have monocytosis greater than 1×10^9/L. In contrast to classical CMML. however. such cases appear to have more immature granulocytes and less dysplasia.

For the majority of cases of CMML the

Table 1. Median Survival (months) of Patients with MDS

Author	RARS	RA	RAEB	RAEB-t	CMML	Overall Median Survival	Number of Patients
Varella et al[48]	53	38	13	3	17	26	56
Goasguen et al[47]	45	32	19	11	15	19	503
Third MIC[32]	51	50	11	5	11	31	1081

Table 2. Percent Leukemic Transformation of MDS

Author	RARS	RA	RAEB	RAEB-t	CMML	Overall Transformation Acute Leukemia
Varella et al[48]	12	15	41	75	33	28
Goasguen *et al*[47]	3	8	20	53	23	17
Third MIC[32]	8	12	44	60	14	23

peripheral blood and bone marrow fulfill the criteria for MDS (variable degrees of trilineage dysplasia) and show the classical chromosomal abnormalities. Monocytes and precursors can be identified in the bone marrow by use of esterase stains (usually a double esterase technique). Although the minimal monocyte count for CMML was established at 1×10^9/L some authors have accepted a diagnosis at a lower threshold.[50,51]

The continued inclusion of CMML in the subtypes of MDS should be based on a unique outcome (either responsiveness, survival, or leukemic progression) similar to those of RAEB. However, a review of 175 patients with CMML showed a survival range of 11 to 60+ months.[32] Stornolio et al[50] demonstrated a major role for blast percentage on survival but not for progression to AML. Fenaus et al[52a] confirmed these observations, whereas Worsley et al[53] emphasized the biologic significance of elevated leukocytes and/or monocytes.

In Storniolo's series[50] patients with more than 0.6×10^9/L monocytes and less than 5% marrow blasts had a median survival of 52.5 months, whereas those with 5% to 20% blasts had a median survival of 15.5 months (similar to RAEB). In a series of 107 CMML cases, Fenaux et al[52a] also noted that patients with an excess of blasts had a short survival, similar to Storniolo's observations. Worsley et al[52] observed that monocytosis greater than 2.6×10^9/L correlated with a poor survival (11 months). The "modified Bournemouth" score was used[54] and patients with high monocyte and neutrophil counts and a high "modified" score had a clinical course resembling that of RAEB.

The presence of unexplained monocytosis, the absence of the Philadelphia chromosome (Ph) or *bcr-abl* fusion gene product in a patient with cytopenia(s) should alert one to consider a diagnosis of CMML.[55] However, there will still be a minority of patients who do not have the Ph' chromosome but demonstrate an abnormal *bcr-abl* gene. Laboratory and clinical features of these patients closely resemble Ph+ CML. Preliminary results from one study[55] suggest a similar response to interferon alfa. Galton" has classified these disorders on morphologic grounds as Ph+CGL, Ph-CGL, and CMML.

Finally, there remains a minority of patients with elevated leukocyte counts but lacking the Ph' chromosome and *bcr-abl* fusion gene. Both Galton and Bennett (unpublished observations) propose that the term atypical CML be reserved for those cases that would have been classified as MDS (usually RAEB). The major distinction is a significant leukocytosis (above 15×10^9/L) with granulocytic dysplasia.

AML WITH TRILINEAGE DYSPLASIA

Because MDS may progress to overt AML in 15% to 20% of cases, it has been suggested that many so called "de novo" AML could represent progression from MDS not previously recognized. The adverse clinical significance of morphologically dysplastic leukemic cells as described in MDS occurring in primary AML has recently been reported by several investigations. In one series 15% of AML cases demonstrated trilineage myelodysplastic features (TMDS) and the remission rate was inferior to AML patients without TMDS.[56] In another series[28] that focused only on dysmegakaryocytopoiesis (DysM) 12% of 95 cases of AML had DysM, with 75% occurring in FAB type M4. Again the complete remission (CR) rate was lower in cases with DysM (14%) compared to those without (82%). In both series TMDS or DysM were not observed in FAB-M3. This finding was confirmed by our experience.[57] However, it appears that dysgranulopoiesis (DysG) is the most significant factor. In our series the CR rate of 336 AML cases was 57% when DysG was present, compared to 71.5% when absent ($P = 0.018$). Chromosome data were not available in these retrospective studies.[28,56] Nonetheless. we demonstrated that

dysplasia in FAB-M1 was associated with an abnormal karyotype and with a low CR rate.[57]

MYELODYSPLASTIC SYNDROMES IN CHILDHOOD

Although MDS have been described primarily in elderly patients and more recently in young adults,[52b] similar biological and clinical features have been observed in children.[58-61] van Wering and colleagues[58] described three cases (2 RAEB-t and 1 CMML) with dysmegakaryopoiesis, hypogranular neutrophils, and a hypercellular marrow. Auer rods were present in one case. A study by Creutzig et al[60] of 21 cases (4 RAEB, 16 RAEB-t, and 1 CMML) revealed evidence of dyserythropoiesis and dysgranulocytic features in each case. Dysmegakaryopoiesis was observed in the majority of patients, and Auer rods were present in 3 of the 16 RAEB-t. The median age was 11 years (range, 2 to 16 years), and the authors concluded that children with MDS might benefit from more aggressive treatment but in general, the survival rate was poor and similar to that observed in adults with MDS. Brandwein et al[61] reported 14 cases of primary MDS (4 RA, 2 RAEB, 1 RAEB-t, 7 CMML), 4 of whom were from two pairs of siblings. The median age was 7 years (range, 1 to 17 years); however, this group was more heterogenous because 7 of the 14 children had CMML.

These studies demonstrate that MDS can be diagnosed in children using the same criteria utilized in adults. The precise frequency is still unclear but MDS may account for approximately 1% to 3% of childhood malignancies. The incidence appears to be increasing with the description of secondary or therapy related myelodysplastic syndromes in children[62] and in

MYELODYSPLASIA AND HUMAN IMMUNODEFICIENCY VIRUS-RELATED DISEASE

Dysplastic maturation of hematopoiesis is a common finding in patients with human immunodeficiency virus (HIV) infection, and dysplastic features in the bone marrow have been described by several authors. Megaloblastic hematopoiesis with dyserythropoiesis, a left shift in granulocytic precursors and a marked increase in marrow megakaryocytes were reported by Spivak et al[64] in 12 HIV-infected patients. In addition, dysplastic bone marrow features were described by Schneider et al[65] in 8 patients. The latter authors demonstrated that all three hematopoietic cell lines were involved in each of the HIV-infected individuals. Karcher et al[66] reported on 216 bone marrows in 178 HIV-infected patients. The most common findings were hypercellularity (53% of specimens) and dysplasia involving at least one cell line (69%) with erythrocytic, megakaryocytic, and dysgranulocytic dysplasia in 56%, 31%, and 18% of specimens, respectively. Dyserythropoietic features included multinucleation, nuclear irregularity, and internuclear chromatin bridge formation. Megakaryocytic dysplasia, such as dwarf forms, nuclear hyposegmentation, and nuclear fragmentation was common. The granulocytic series showed asynchrony between nuclear and cytoplasmic maturation; occasional marrow aspirates exhibited multinucleation or hypogranular maturing cells.

The mechanism(s) for HIV-related myelodysplasia is not clear. Drug toxicity, a secondary effect of opportunistic infections, or HIV infection itself have all been proposed as causative factors. Karcher et al[66] reported a significant correlation between myelodysplasia and Centers for Disease Control class IV disease and a history of opportunistic infection. These authors concluded that myelodysplasia in HIV-infected patients is probably directly related to HIV infection, which worsens with disease progression and is not a side effect of therapy.[66] It should be emphasized that dysplastic morphologic changes in HIV-infected patients do not necessarily have the same clinical implications as myelodysplasia in the non-HIV setting in regard to the evolution to acute leukemia.[65]

REFERENCES

1. Block M, Jacobson LO, Bethard WF: Preleukemic acute leukemia. JAMA 152:1018-1023, 1953

2. Rheingold JJ, Kaufman R, Adelson E, et al: Smouldering acute leukemia. N Engl J Med 268:812-816, 1963

3. Bomford RR, Rhodes CP: Refractory anaemia. I. Clinical and pathological aspects. II. Aetology and treatment. Q J Med 10:174-281, 1941

4. Vilter RS, Will JJ, Jarrold T: Refractory anemia with hyperplastic bone marrow (a regenerative anemia). Semin Hematol 4:175-193, 1967

5. Dacie JV, Smith MD, White JC, et al: Refractory normoblastic anaemia: A clinical and haematological study of 7 cases. Br J Haematol 5:56-82, 1959

6. Lewis SM, Venvilghen RL: Dyserythropoiesis and dyserthropoietic anemia. Brit J Haematol 23:1-4, 1972

7. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the acute leukemias. Br J Haematol 33:329-331, 1976

8. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 51:189-199, 1982

9. Bennett JM, Catovsky D, Daniel MT, et al: Proposed revised criteria for the classification of acute myeloid leukemia. Ann Intern Med 103:626-629, 1985

10. Amenomori T, Tomonaga M, Jinnai I, et al: Cytogenetic and cytochemical studies on progenitor cells of primary acquired sideroblastic anemia (PASA): Involvement and mosaicism with normal clone. Blood 70:1367-1372, 1987

11. Janssen JWG, Buschle M, Layton M, et al: Clonal analysis of myelodysplastic syndromes: Evidence of multipotent stem cell origin. Blood 73(1):248-254, 1989

11a. Doll DC, List AF, Dayhoff DA, et al: Acanthocytosis associated with myelodysplasia. J Clin Oncol 7:1569-1572,1989

12. Dacie JV, Mollin KL: Siderocytes, sideroblasts and sideroblastic anaemia. Act Medica Scand 179:237-248, 1966 (suppl 445)

13. Bessis MC, Jensen WN: Sideoblastic anaemia, mitochondria and erythroblastic iron. Br J Haematol 11:499-451, 1965

14. May A, DeSouza P, Barnes K, et al: Erythroblast iron metabolism in sideroblastic marrows. Br J Haematol 52:611-612,1982

15. Hillman RS, Finch CA: Red Cell Manual (ed 4). Philadelphia, PA, Davis, 1974, p 4

16. Galton DAG: The myelodysplastic syndromes. Scand J Hematol 36:16-20, 1986(suppl 45)

17. Juneja SK, Imbert M, Jouault H, et al: Haematological features of primary myelodysplastic syndromes (PMDS) at initial presentation. A study of 118 cases. J Clin Pathol 36:1129-1135, 1983

18. Cazzola M, Barosi G, Gobbi PG, et al: Natural history of idiopathic refractory sideroblastic anemia. Blood 71(2):305-312,1988

19. Hast R, Nilsson I, Widell S, et al: Diagnostic significance of dysplastic features of peripheral blood polymorphs in myelodysplastic syndromes. Leukemia Res 13(2):173-178, 1989

20. Gustke SS, Becker GA, Garancis JC, et al: Chromatin clumping in mature leukocytes. A hitherto unrecognized abnormality. Blood 35:637-658, 1970

21. Felman P, Bryon PA, Gentilhomme O, et al: The syndrome of abnormal chromatin clumping in leuccocytes: A myelodysplastic disorder with proliferative features? Br J Haematol 70:49-54, 1988

22. Jaen A, Irriguible D, Milla F, et al: Abnormal chromatin clumping in leucocytes: A clue to a new subtype of myelodysplastic syndrome. Eur J Haematol 45(4):209-214,1990

23. Langenhuijsen MMAC: Neutrophils with ring-shaped nuclei in myeloproliferative disease. Br J Haematol 58:227-230,1984

24. Van der Weide M, Sizoo W, Krefft J, et al: Myelodysplastic syndromes: Analysis of morphological features related to the FAB classification. Eur J Haematol 41:58-61, 1988

25. Boogaerts MA, Nelissen V, Roelant C, et al: Blood neutrophil function in primary myelodysplastic syndromes. Br J Haematol 55:217-227, 1983

26. Bendix-Hansen K, Kerndrup G: Myeloperoxidase-deficient polymorphonuclear leukocytes. V. Relation to neutrophil alkaline phosphatase activity and FAB classification in the primary myelodysplastic syndrome. Scand J Haematol 35:197-200, 1985

27. Kawaguchi M, Nehashi Y, Aizawa S, et al: Comparative study of immunotycochemical staining versus Giemsa stain for detecting dysmegakaryopoiesis in myelodysplastic syndromes (MDS). Eur J Haematol 44(2):89-94, 1990

28. Jinnai I, Tomonaga M, Kuriyama K, et al: Dysmegakaryocytopoiesis in acute leukemias: Its predominance in myelomonocytic (MA) leukaemia and implication for poor response to chemotherapy. Br J Haematol 66:467-472, 1987

29. Wong KF, Chan JKC: Are "dysplastic" and hypogranular megakaryocytes specific markers for myelodysplastic syndromes? Br J Haematol 77(4):509-514, 1991

30. Scott CS, Cahill A, Bynoe AG, et al: Cytochemistry in primary myelodysplastic syndromes and myeloblastic anaemias: Demonstration of normal staining patterns associated with dysmyelopoiesis. Br J Haematol 55:411-418, 1983

31. Second MIC Cooperative Study Group: Morphologic, immunologic and cytogenetic (MIC) working classification of acute myeloid leukemias. Cancer Genet Cytogenet 30:1-5, 1988

32. Third MIC Cooperative Study Group: Morphologic, immunologic and cytogenetic (MIC) working classification of the primary myelodysplastic syndromes and therapy related myelodysplasias and leukemias. Cancer Genet Cytogenet 32:1-10, 1988

33. Ascensai JL, Kay NE, Wright JJ, et al: Lymphoblastic transformation of myelodysplastic syndrome. Amer J Hematol 22:431-434, 1986

34. Geller RB, Zahurak M, Hurwitz CA, et al: Prognostic importance of immunophenotyping in adults with acute myelocytic leukaemia: The significance of the stem-cell glycoprotein CD34 (MY10). Br J Haematol 76:340-347, 1990

35. Kristensen JS, Hokland P: Monoclonal antibody ratios in malignant myeloid diseases: Diagnostic and prognostic use in myelodysplastic syndromes. Br J Haematol 74:270-276, 1990

36. Guyotat D, Campos L, Thomas X. et al: Myelodysplastic syndromes: A study of surface markers and in vitro growth patterns. Am J Hematol 34(1):26-31, 1990

37. Sanz GF, Sanz MA, Vallespi T. et al: Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes. A multivariate analysis of prognostic factors in 370 patients. Blood 74(1):395-408, 1989

38. Goasguen JE, Bennett JM, Cox C. et al: Prognostic implication and characterization of the blast cell population in the myelodysplastic syndrome. (in press)

39. Tricot G, DeWolf-Peeters C, Vlietinck R, et al: Bone marrow histology in myelodysplastic syndromes. II. Prognostic value of abnormal localization of immature precursors in MDS. Br J Haematol 158:217-225, 1984

40. Sultan C: Dysmyelopoietic syndromes. in Gralnick HR: Classification of acute leukemia. Ann Intern Med 87:740-753, 1977

41. Pagliuca A, Layton DM, Manoharan A, et al: Myelofibrosis in primary myelodysplastic syndromes: A clinicomorphological study of 10 cases. Br J Haematol 71:499-504, 1989

42. Gatterman N, Aul C, Schneider W: Two types of acquired idiopathic sideroblastic anaemia (AISA). Br J Haematol 74(1):45-52, 1990

43. Hasegawa **Y,** Sakai N, Toyama M, et al: Chronic myelomonocytic leukemia transformed from refractory anemia with ring sideroblasts with a rare abnormal chromosome, inv(12). Rinsho-Ketsueki 31(1):75-79, 1990

44. Tricot G, Boogaerts MA, DeWolf-Peeters C, et al: The myelodysplastic syndromes: Different evolution patterns based on sequential morphological and cytogenetic investigations. Br J Haematol 59:659-670, 1985

45. Tricot G, Vlietinck R, Boogaerts MA, et al: Prognostic factors in the myelodysplastic syndromes: Importance of initial data on peripheral blood counts. bone marrow cytology, trephine biopsy and chromosomal analysis. Br J Haematol 60:19-32, 1985

46. Weisdorf DJ, Oken MM, Johnson J, et al: Chronic myelodysplastic syndrome: Short survival with or without evolution to acute leukaemia. Br J Haematol 55:691-700, 1983

47. Goasguen J-E, Garand R, Bizet **M,** et al: Prognostic factors **of** myelodysplastic syndromes—A simplified 3-D scoring system. Leukemia Res 14(3):255-262, 1990

48. Varella BL, Chuang C, Woll JE, et al: Modifications in the classification of primary myelodysplastic syndromes: The addition of a scoring system. Hematol Oncol 3:55-63, 1985

49. Cason JD, Trujillo JM, Estey EH, et al: Peripheral acute leukemias: High peripheral but low marrow blast count. Blood 74(5):1758-1761, 1989

50. Storniolo AM, Moloney WC, Rosenthal D, et al: The chronic myelodysplastic syndromes. Leukemia 4(11):766-770,1990

51. Miescher PA, Farquet JJ: Chronic myelomonocytic leukemia in adults. Semin Hematol 11:129-139. 1974

52a. Fenaux P, Benscart R, Lai JL, et al: Prognostic factors in adult chronic myelomonocytic leukemia: Analysis of 107 cases. J Clin Oncol 6:1417-1424, 1990

52b. Fenaux P, Estienne MH, Morel P, et al: De novo myelodysplastic syndromes (MDS) in adults aged 50 or less. Clinical course and comparison with older patients. Blood 76:10, 1990(suppl 1)

53. Worsley A, Oscier DG, Stevens J, et al: Prognostic features of chronic myelomonocytic leukaemia: A modified Bournemouth score gives the best prediction of survival. Br J Haematol 68:17-21, 1988

54. Mufti GJ, Stevens JR, Oscier DG, et al: Myelodysplastic syndromes: A scoring system with prognostic significance. Br J Haematol 59:425-433, 1985

55. Kantarjian HM, Shtalnid M, Karzrock R, et al: Significance and correlation of molecular analysis results in patients with Philadelphia chromosome negative chronic myelogenous leukemia and chronic myelomonocytic leukemia. Am J Med 85:639-644, 1988

56. Brito-Babapulle F, Catovsky D, Galton DAG: Clinical and laboratory features of de novo acute myeloid leukaemia with trilineage myelodysplasia. Br J Haematol 66:445-450, 1987

57. Goasguen JE, Matsuo T, Cox C, et al: Evaluation of the dysmyelopoiesis in 336 patients with "de novo" acute myeloblastic leukemia: Major importance of dysgranulopoiesis for remission and survival (an ECOG study) (submitted)

58. van Wering ER, Kamps WA, Vossen JM, et al: Myelodysplastic syndromes in childhood: Three case reports. Br J Haematol 60:137-142, 1985

59. Wegelius R: Preleukemic states in children. Scand J Haematol 36:133-139, 1986 (suppl 45)

60. Creutzig **U,** Cantu-Rajnoldi A, Ritter J, et al: Myelodysplastic syndromes in childhood. Report of 21 patients from Italy and West Germany. Am J Ped Hematol/Oncol 9(4):324-330, 1987

61. Brandwein JM, Horsman DE, Eaves AC, et al: Childhood myelodysplasia: Suggested classification as myelodysplastic syndromes based on laboratory and clinical findings. Am J Ped Hematol/Oncol 12(1):63-70, 1990

62. Pui CH, Hancock ML, Raimondi SC, et al: Myeloid neoplasia in children treated for solid tumors. Lancet 336(8712):417-421, 1990

63. Kantarjian HM, Keating MJ: Therapy-related leukemia and myelodysplastic syndrome. Semin Oncol 14(4):435-443, 1987

64. Spivak JL, Selonick SE, Quinn TC: Acquired immunodeficiency syndrome and panctyopenia. JAMA 250:3084-3087,1983

65. Schneider DR, Picker LJ: Myelodysplasia in the acquired immune deficiency syndrome. Am J Clin Pathol 84:144-152, 1985

66. Karcher **DS,** Frost AR: The bone marrow in human immuno-deficiency virus (HIV)-related disease. Am J Clin Path 95(1):63-71, 1991