

MORPHOLOGY AND CLASSIFICATION OF THE MYELODYSPLASTIC SYNDROMES AND THEIR PATHOLOGIC VARIANTS

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Historical Background/Introduction

Despite the suffix *-dysplastic*, the term myelodysplastic syndrome (MDS) refers to a clonal disorder of the hematopoietic stem cell interrelated with other clonal bone marrow disorders such as the acute leukemias and the myeloproliferative syndromes (Figure 1). The various subtypes of the myelodysplastic syndromes can be clinically 'lumped' together as they have in common⁽⁶⁴⁾:

- (i.) the clinical manifestation of bone marrow failure as well as a tendency to transform into an acute leukemic phase
- (ii.) the pathological manifestation of morphological abnormalities (termed "dysplasia") of the peripheral blood and bone marrow cells such as ringed sideroblasts, megaloblastic erythroid precursors, hypogranulation/hyposegmentation of the granulocytes and micromegakaryocytes.⁽⁶²⁾

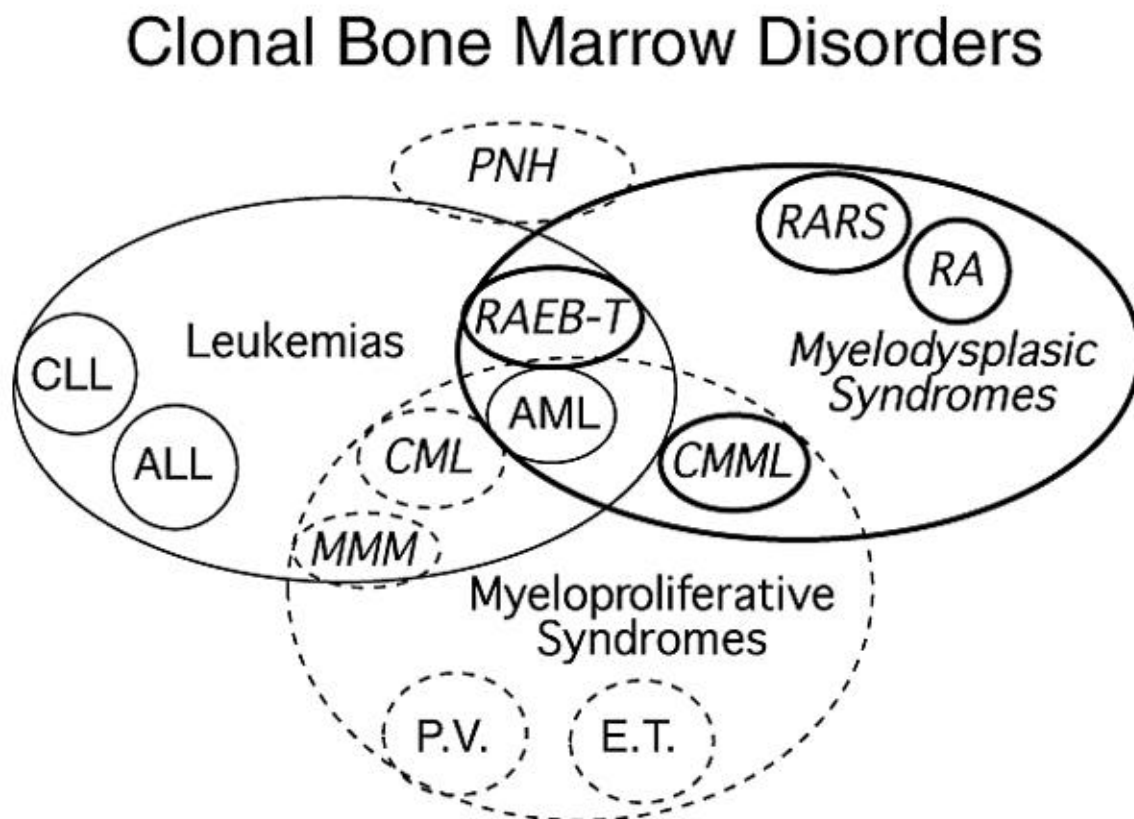


Figure 1: Clonal bone marrow disorders.

Abbreviations: LEUKEMIA- acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL); MYELOPROLIFERATIVE SYNDROMES- chronic myelogenous leukemia (CML), myeloid metaplasia myelofibrosis (MMM), polycythemia vera (PV), essential thrombocythemia (ET); MYELOYDYSPLASTIC SYNDROMES- refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), chronic myelomonocytic leukemia (CMML), paroxysmal nocturnal hemoglobinuria (PNH)

The above description serves as a clinico-pathological definition of MDS; the pathological manifestation reminds the reader that for lack of dependable, reproducible markers of clonality, the morphological abnormalities noted represent in part a working definition of the disorder. The above clinical manifestation reminds the reader that this is a syndrome with a wide range of presentation, specifically of cytopenias that can range from an isolated anemia for 10 years to a rapidly evolving acute leukemia fatal within weeks. It is not surprising then that this disease has defied proper classification over the years. Consequently, the medical literature is replete with many descriptive terms developed prior to the widespread use of the term MDS⁽⁶⁴⁾: herald state of leukemia, refractory anemia, preleukemic anemia, preleukemic syndrome, preleukemia, refractory anemia with ringed sideroblasts, refractory normoblastic anemia, refractory anemia with excess myeloblasts, smoldering acute leukemia, chronic erythemic myelosis, subacute myelomonocytic leukemia, hypoplastic acute myelogenous leukemia, hematopoietic dysplasia, subacute myeloid leukemia.

In 1949, Hamilton-Patterson⁽⁴⁵⁾ described three patients with acute leukemia preceded by an anemic phase (“preleukemic anemia”). This observation was followed in 1953 by a report by Block et al⁽¹²⁾ of a larger group of 12 patients with a cytopenic phase of whom 11 later developed acute leukemia. Since these initial series of patients described in the literature were mostly comprised of patients whose course culminated in acute myelogenous leukemia (AML), the full spectrum of cytopenia with bone marrow dysplasia was not described, as in general only 20% to 30% of all patients now termed as MDS progress to overt, acute leukemia.

In 1975, the French-American-British (FAB) group in their initial proposals for the morphological classification of the acute leukemias,⁽⁸⁾ acknowledged that not all patients with cytopenias and dysplastic peripheral blood and bone marrow features progress to acute leukemia. A distinction was made between acute leukemia with its rapid onset of signs and symptoms requiring immediate treatment and a group of disorders that showed some of the characteristics of AML but were subacute or chronic in nature. The FAB group chose the term *dysmyelopoietic or myelodysplastic syndromes* for this latter group of disorders, as unlike AML, immediate treatment was rarely needed and these patients were typically fifty years of age or older. Initially, the FAB group recognized two categories of MDS: “refractory anemia with excess blasts” (RAEB) and “chronic myelomonocytic leukemia” (CMML). It was noted that a variable progression of these

cases evolved to overt acute leukemia associated with an increase in blasts to approximately greater than 30%. In 1980, a larger number of cases were reviewed with the intent to determine if specific morphological abnormalities, singly or in groups, would predict for a different biological outcome. This larger review of cases led to an expanded definition of the myelodysplastic syndromes into five subgroups that could be characterized by dysplastic features noted above.⁽⁹⁾

Laboratory Presentation and Diagnosis of MDS

The diagnosis should be entertained particularly in an elderly patient (the peak incidence⁽⁹⁸⁾ is in the eighth decade of life!) in the setting of an unexplained anemia, neutropenia, thrombocytopenia and/or monocytosis without the usual explanations of marrow failure. Anemia (hemoglobin < 11 g/dl) is most common (typically isolated), but occasionally isolated thrombocytopenia and even less commonly isolated neutropenia have been noted. Isolated thrombocytopenia may precede by 2-10 years the development of the features to be discussed below that permit classification as MDS.^(75,82) Another challenge to the clinician confronting a potential case of MDS is that, occasionally, the patient will not present with cytopenia. The presentation can be one of leukocytosis, particularly in association with CMML, or one of thrombocytosis, particularly in association with refractory anemia or refractory anemia with ringed sideroblasts (in turn in association often with partial deletion of the long arm of chromosome 5, termed “5q-”),^(74,120)

The diagnosis of MDS can be made only after careful examination of the peripheral blood smear, bone marrow aspirate and biopsy. No single morphological finding is diagnostic; rather, the combination of dysplastic features in the peripheral blood and bone marrow is necessary. It must be emphasized that the diagnosis of MDS is a diagnosis of exclusion. In particular, the following always must be excluded⁽⁶⁴⁾ as they can be accompanied by dysplasia:

- i. vitamin B12 and/or folate deficiency
- ii. proven exposure to heavy metals⁽⁹³⁾
- iii. recent cytotoxic therapy
- iv. ongoing inflammation including HIV^(46,56,59) and cancer⁽¹⁴⁾
- v. chronic liver disease/alcohol use^(16,43)

The first three should be considered absolute exclusions, thus precluding the definite diagnosis of MDS. The latter two could be considered to be relative exclusions as there will be patients with both MDS and a coincidental inflammatory state (such as cancer or rheumatoid arthritis) or MDS with coincidental chronic liver disease/alcohol use. Furthermore, it should be emphasized that even after ruling out the above conditions, the diagnosis of MDS can be elusive given the variability⁽⁵⁾ (i) in sampling the sternal site versus the iliac site; (ii) in cellularity that can even be noted in adjacent marrow spaces of the same core biopsy; (iii) over time in the same patient; and (iv) in involvement of the erythroid, myeloid and megakaryocytic lineages. Classically there is

trilineage dysplasia but occasionally, particularly in early-onset cases, there can be dysplasia confined to only one or two lineages.

The standard stains (May-Giemsa, hematoxylin and eosin) should be done as well as the Prussian blue stain for iron and the reticulin stain for fibrosis. If the patient is iron deficient based on the Prussian blue stain, a silver stain⁽¹¹⁰⁾ may reveal ringed sideroblasts that would otherwise be masked by iron deficiency, as the silver stain demonstrates only the phosphate moiety.

There are several cytochemical and immunologic techniques that can supplement the above standard stains.⁽⁹⁸⁾ The myeloid origin of the blast cells can usually be confirmed by the peroxidase and Sudan Black B stains, while the non-specific esterase or double-esterase stain can often distinguish early monocytic precursors from poorly granulated myelocytes. The double esterase stain may also identify a population of early myeloid/monocytic cells (presence of both granulocytic and monocyte esterase) in the marrow.⁽¹⁰⁰⁾ In a study from the Mayo Clinic, the iron stain was the most useful cytochemical stain in distinguishing certain types of MDS cases from cases in the non-MDS and non-diagnostic groups.⁽¹⁰¹⁾ It should be noted that the peroxidase decreases in each cell and amount over the course of MDS.^(23,97)

The application of immune marker analysis of lymphoid and myeloid cells in the diagnosis of the acute leukemias has naturally found use in the diagnosis of the myelodysplastic syndromes. Several immunologic phenotypes have been described using a battery of monoclonal antibodies: the most common is “myeloid” (CD13+, CD14+, CD33+, peroxidase+), but both pure lymphoid blast types⁽⁶³⁾ (TdT+, CD19+, CD10+) and biphenotypic patterns have been noted. Several flow cytometric studies of bone marrow aspirates in MDS the past ~5 years have assayed for the early marker of stem cell/myeloid differentiation, CD34.^(42,54) Immunohistochemical staining of the bone marrow biopsy can also be done for CD34 expression.^(78,84,105) In these studies, there has been a correlation of CD34 positivity with RAEB and refractory anemia with excess blasts in transformation (RAEB-T) subtypes, with CD34 positivity significantly associated with progression to leukemia and shorter survival. In a study by Oertel et al,⁽⁸⁴⁾ the blasts in the RAEB subtype were predominantly CD34 negative with an emergence of CD34 positive blasts in the RAEB-T subtype. Along those lines, the finding of CD34 positivity or a phenotype such as the co-expression of CD33/CD13 may prompt the clinician to consider similar “induction-remission” therapy as used in *de novo* AML. Such a situation was reported by Woodlock et al:⁽¹³¹⁾ two cases of CMML that expressed CD34 positivity, one of the cases also had aberrant expression of CD3 (a T cell marker). This co-expression and the CD34 positivity were both felt to be consistent with aggressive, proliferative disease, thus prompting the authors to administer AML-like induction-remission therapy. A complete remission was achieved in each case. Another aggressive clinical subset of MDS with an immunophenotypic correlate are those cases of MDS clearly related to organochemical exposure. Such cases have a high expression of glycoprotein (gp) p-170, the product of the multidrug resistance gene-1 (as well as CD34 positivity).⁽¹⁰⁶⁾ However, in these cases of p-170 expression⁽⁶⁸⁾ or for that matter CD34 positivity, intensive chemotherapy, though possibly achieving a complete remission, will usually not be curative since the “remission” hematopoiesis will still in all likelihood be clonal, as the MDS phenotype typically involves an early stem cell, i.e., CD34+.

Immunologic techniques have been also applied towards characterization of megakaryocytes in MDS. Occasionally in MDS, the megakaryocytes cannot be easily identified by light microscopy. In particular, the abnormally small megakaryoblasts (“dwarf cells”) may resemble lymphoid precursors similar to FAB L2 lymphoblasts. In one study of 23 patients with MDS where 12/23 (52%) had dysmegakaryopoiesis on routine May-Giemsa staining, an additional nine cases of MDS demonstrated dysmegakaryopoiesis after staining the megakaryocytes for GP IIb/IIIa, “CDw41” by the alkaline phosphatase anti-alkaline phosphatase technique. Furthermore, this immunostain also detected megakaryoblasts in that study, where none were detected by May-Giemsa staining.⁽⁶⁰⁾ Other immunostains that can easily identify megakaryocytes on air-dried smears include an antibody prepared against platelet specific gp IIIa alone (CD61)⁽¹¹²⁾ or by histologic bone marrow reactions with an antibody against factor VIII⁽¹⁰⁾ or fibronectin.⁽⁹⁸⁾ Erythroid progenitors also can be identified by a variety of immunostains with antibodies against glycophorin A, hemoglobin, CD45 and transferrin receptor CD71.⁽⁹⁸⁾ The identification of erythroblasts by immunostaining may be of prognostic significance as there may be a higher incidence of transformation to erythroleukemia.⁽²¹⁾

Despite the many cyto-immunological tests available on the marrow aspirate, the need for careful examination of the bone marrow biopsy by routine light microscopy should not be trivialized. The definition of dysplasia (as defined by Bartl et al⁽⁵⁾) as “a loss in uniformity of the individual cells, as well as a loss in their architectural orientation,” reminds one that the biopsy is necessary for the full delineation of MDS. The core biopsy can complement examination of the aspirate in the diagnosis as well as the prognosis⁽⁷¹⁾ of MDS in several ways⁽⁵⁾:

- In cases of inadequate marrow aspiration, the core biopsy still usually allows for determination of the subgroups of MDS.^(115,129) Furthermore, there appears to be a good concordance between the proportion of marrow blasts in the core biopsy and the aspirate. In one particular study showing such a correlation,⁽²⁵⁾ the histologic (biopsies) and cytological (marrow smears) examinations were concordant in 24 of 28 cases by the FAB classification.
- Identification of clusters of immature cells that are myeloid in origin by cyto- or immunohistochemistry displaced from the peritrabecular area to the intertrabecular areas.⁽¹¹⁶⁾ The finding of abnormal localization of immature precursors (ALIP) may possibly confer a poor prognosis,⁽¹¹⁶⁾ but there is no clear-cut consensus⁽⁶⁹⁾
- Easier identification of dysmegakaryopoiesis than by the marrow aspirate. Approximately 80% of biopsies demonstrate dysmegakaryopoiesis. Furthermore, the severity of dysmegakaryopoiesis may confer a worse prognosis.⁽⁹⁵⁾
- Ability by core biopsy to determine the degree of marrow fibrosis. Approximately 50% of cases will have a mild to moderate increase in marrow reticulin.^(95,115) Cases with marked fibrosis^(66,71,86,88,108) will be discussed later as such cases may have prognostic and therapeutic implications.
- Accurate assessment of the marrow cellularity. The bone marrow cellularity should be at least normocellular for the age of the patient. Typically, it is hypercellular particularly in the CMML, RAEB, and RAEB-T subgroups.⁽⁴⁹⁾ However, there are cases of hypoplastic MDS to be discussed later. The core biopsy can also help in

distinguishing this from cases of hypocellular marrow with foci of blasts (“hypocellular AML”).^(24,50)

Table 1. Checklist of morphological features of MDS.

	Bone Marrow and/or Peripheral Blood Findings
? Dyserythropoiesis	Bone Marrow -multinuclearity -nuclear fragments -megaloblastoid changes -cytoplasmic abnormalities -ringed sideroblasts -increased erythroblasts Peripheral blood: -poikilocytosis -anisocytosis -nucleated red blood cells
? Dysgranulopoiesis	Nuclear abnormalities including: -hypolobulation -nuclear sticks -ring-shaped nuclei hypogranulation
? Dysmegakaryopoiesis	micromegakaryocytes large mononuclear forms multiple small nuclei reduced numbers

Morphological Characteristics (Table 1)

The *sine qua non* in the diagnosis of MDS is trilineage dyspoiesis. This dyspoiesis results from clonal expansion of a multipotent stem cell leading to impaired differentiation, resulting clinically in cytopenia. The impaired differentiation may be on the basis of extensive apoptosis.⁽⁹¹⁾ The underlying clonal expansion of MDS was first suggested by Dacie,⁽²²⁾ who noted a dimorphic population of red cells consistent with a clonal disorder. Years later, this was supported by studies of glucose-6-phosphate dehydrogenase mosaicism and cytogenetic studies that have demonstrated an abnormal karyotype in the dysplastic cells coexisting with residual marrow cells with a normal karyotype.⁽²⁾ These laboratory studies^(2,91) demonstrating clonality remind us that though we use the term dysplasia in describing the morphological abnormalities, the underlying process is neoplastic and not dysplastic in the strict sense of the term.

The following section is a compilation of morphological abnormalities (dysplasia) used to define the myelodysplastic syndromes. In general, these abnormalities should be present in at least 10% or greater of cells of the respective lineage in consideration. The actual subgroup of MDS then can be determined in considering four features after one is convinced that there is an adequate degree of dysplasia:

- percent ringed sideroblasts
- percent bone marrow blasts
- absolute number of peripheral blood monocytes
- presence of Auer rods

An algorithm of the semi-quantitative diagnosis of MDS by the FAB criteria is presented in Figure 2.

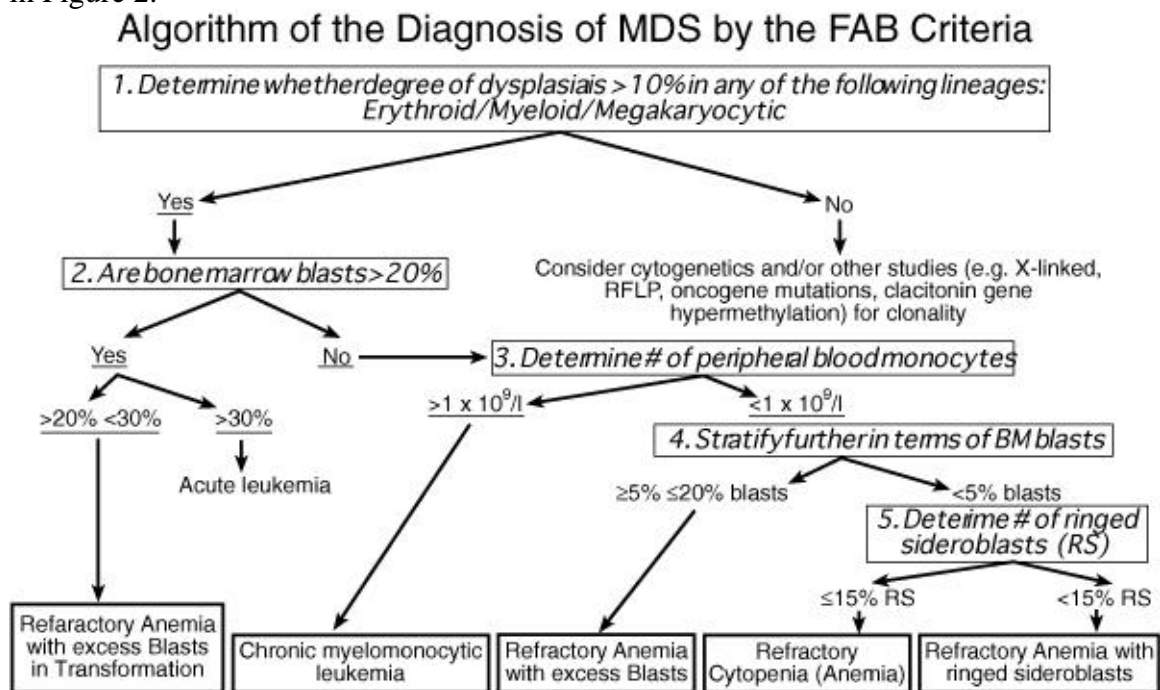


Figure 2. Algorithm of the diagnosis of MDS by the FAB criteria.

Dyserythropoiesis

The complete blood cell count can often suggest the presence of MDS in terms of a moderate macrocytosis (mean cell volume reported in the 100-110 fm range). MDS may account for 5% of all cases evaluated for macrocytosis.⁽¹⁸⁾ Other changes suggestive of MDS from the peripheral blood include basophilic stippling, fragmented cells and occasionally nucleated red cells. The circulating nucleated red cells, in turn, often have dysplastic features.

Not surprisingly, the morphological abnormalities in the erythroid lineage are more pronounced in the bone marrow than the peripheral blood. The two most characteristic features⁽⁵⁾ are megaloblastosis (i.e., fine chromatin with asynchronous cytoplasm) and the presence of ringed sideroblasts. Other findings include multinuclear

fragments, bizarre nuclear shapes, internuclear bridging,⁽⁴⁸⁾ mitosis, abnormal dense chromatin and abnormal cytoplasmic features. These cytoplasmic abnormalities may include intense basophilia, Howell-Jolly bodies and ghosted cytoplasm. In regards to the latter, on routine May-Giemsa staining, erythroblasts with areas of unstained cytoplasm (“ghosted”) with ill-defined edges coexisting with coarse basophilic stippling appear to represent ringed sideroblasts.⁽¹⁾

A leftward shift in erythropoiesis can be noted, with the number of erythroid precursors between 5-50%. If more than 50%, then the diagnosis is erythroleukemia if there are more than 30% blasts (all nucleated cells or nonerythroid component).⁽⁹⁾

The finding of bone marrow sideroblasts is not necessarily diagnostic for MDS as normal marrows can have occasional erythroblasts with iron granules (but these sideroblasts typically have fewer than five granules), and sideroblasts can be noted in a variety of pathologic states to be discussed herein. By definition, pathologic sideroblasts have five or more granules/cell and can be termed “ringed” sideroblasts if the granules cover more than one-third of the nuclear rim.⁽⁴⁷⁾ Cases with clusters of ferritin granules, of more than five/cell but not surrounding the nucleus also have been noted. Historically, these would not be counted with the ringed sideroblasts as pathologic, but in our opinion they are pathologic, and so should be included.

Ringed sideroblasts and increased iron storage may be found in any of the MDS, but they are characteristic of refractory anemia with ringed sideroblasts (RARS). Yet, the ringed sideroblast is not synonymous with MDS as it can be noted in other pathologic conditions, such as alcohol-induced sideroblastic anemia and chemotherapy-induced anemia and in cases of the myeloproliferative syndromes.⁽³⁰⁾ There also appears to be a separate entity of sideroblastic anemia confined to dyserythropoiesis only, termed pure sideroblastic anemia (PSA).^(16,36,47) The difference with RARS is that in RARS there must also be dysplasia in the myeloid and/or megakaryocytic lineages. The distinction between these two entities (PSA and RARS) is important given the approximately fourfold increase in leukemic progression in patients with RARS compared with pure sideroblastic anemia (dyserythropoiesis without dysgranulopoiesis and/or dysmegakaryopoiesis).^(36,121) The distinction between RARS and other similar states of MDS with < 5% blasts is also important for prognostic purposes. In common, they have unequivocal dyserythropoiesis with a variable degree of dysmegakaryopoiesis/dysgranulopoiesis, with the difference being the degree of sideroblastosis - the FAB group chose a level of 15%. Cases less than that were termed refractory anemia (RA) and cases greater than or equal to 15% were termed RARS. Initially all nucleated cells were considered instead of only erythroblasts given the difficulty in identifying just nucleated erythroid precursors with the nuclear counterstains originally employed (Neutral red). Since then, this definition has been revised to refer strictly to erythroblasts.⁽³⁴⁾ The result can be a shift of patients classified as RA to RARS. This lower limit may be reasonable with the use of appropriate nuclear counterstains for erythroid precursors. Yet, it appears that the majority of patients with RARS far exceed the 15% limit.⁽⁵⁵⁾

Dysgranulopoiesis

The two characteristic peripheral blood findings are hypogranulation and hyposegmentation of the polymorphonuclear leukocytes with chromatin condensation

(Pelger-Huët-like anomaly, also termed “pelgeroid”). The hypogranulation can be extreme to the point that the granules are absent with resultant negative peroxidase reaction.^(23,98)

Hast et al have quantified the degree of dysgranulopoiesis with a scoring system that grades the degree of hypogranulation and hypolobulation. In a series of 51 cases of MDS, they noted that 43/51 (84%) cases had hypogranulation and 49/51 (96%) cases had hypolobulated neutrophils (“pelgeroid polymorphs”). There was a very good correlation between the degree of hypolobulation and/or hypogranulation in the peripheral blood compared to the bone marrow. This is useful to know in cases of suspected MDS where a bone marrow cannot be readily obtained. Several other positive correlations were noted: degree of hypogranulation and increased percentage of bone marrow blasts, degree of hypolobulation and ringed sideroblasts, degree of hypolobulation and bone marrow fibrosis, and degree of hypolobulation and complex chromosomal abnormalities.⁽¹²⁷⁾

Besides hypogranulation, other cytoplasmic abnormalities include persistent cytoplasmic basophilia of the rim of the cell and occasionally hypergranulation instead of hypogranulation and larger granules than usual. The latter can recapitulate the appearance of neutrophils in the congenital disorder Chédiak-Higashi Syndrome.

Several nuclear abnormalities have been noted besides hypolobulation. Clumping of chromatin has been described where blocks are separated by a clear space leading to an appearance of nuclear fragmentation associated with a loss of segmentation. These patients have variable leukocytosis, with survival typically less than a year.^(31,53) Further cases are needed to determine whether this entity is best classified as MDS or a myeloproliferative disorder. Ring-shaped nuclei have been described in MDS as well as myeloproliferative disorders. In one series, ringed granulocytic nuclei were noted in a quarter of cases with MDS.⁽⁶⁷⁾ Nuclear sticks can be seen, particularly in cases of secondary MDS or therapy-related MDS.

The above morphological characteristics may explain in part the tendency of these patients towards infection. Infection is the most common cause of death in MDS, far more common a cause of death than leukemic transformation.⁽⁸⁹⁾ Phagocytic adhesion, chemotaxis and microbicidal capacities are impaired.⁽⁹⁶⁾ However, no correlation of infection with the degree of hypogranulation has been found.⁽⁹⁶⁾ But the risk for fatal infection appears to correlate with the subtype; namely, there is a higher risk for fatal infection if the subtype is RAEB, RAEB-T or CMML compared with RA or RARS.⁽⁸⁵⁾ An increase in the percentage of blasts may also correlate with the risk of fatal infection.⁽⁸⁵⁾

Dysmegakaryopoiesis

As in the case of dysgranulopoiesis, qualitative findings are more notable than quantitative findings. The number of megakaryocytes are usually normal, though hypoplasia or hyperplasia can occasionally be seen. MDS with megakaryocytic hyperplasia can be confused with idiopathic thrombocytopenic purpura. In the peripheral blood, large hypogranular or hypergranular platelets can be seen. In the marrow, marked morphologic abnormalities of the megakaryocytic precursors can be seen in at least half of the patients; as mentioned previously, if immunostains are employed,

dysmegakaryopoiesis will be detected in almost all cases. Ideally, at least 10 megakaryocytes should be assessed. Dysmegakaryocytic features include:

- Micromegakaryocytes (“dwarf forms”), which can be defined as two times less than the diameter of a neutrophil (<800 µm/m²). Micromegakaryocytes in combination with pelgeroid granulocytes may be the most specific dysplastic markers of MDS.⁽⁶⁵⁾
- Multiple small nuclei that are reminiscent of the neutrophils of megaloblastic anemia.
- Mononuclear forms, large or small. A small mononuclear form with a round nucleus eccentrically placed has been noted in association with the cytogenetic abnormality, 5 q-⁽¹¹¹⁾
- Hypogranulated megakaryocytes.⁽¹³⁰⁾ A result may be a deficiency in the dense granules of the mature platelet leading to platelet dysfunction.⁽³⁷⁾

As such, clinically these morphological abnormalities can be accompanied by a tendency towards bleeding despite a normal platelet count,⁽⁹⁰⁾ though commonly the risk for bleeding correlates with the degree of thrombocytopenia but it may also correlate with the degree of dysmegakaryopoiesis. A correlation between prolongation of the bleeding time and an increase in micromegakaryocytes >10% has been reported.⁽⁷⁹⁾

Blast Cell Characteristics in MDS

In the diagnosis of MDS, it's very important to have an unambiguous definition of blast cells given the fact that the percentage of blast cells is the single most important prognostic factor in MDS in terms of overall survival and risk of overt leukemic progression.^(3,17,40,80,97) The prognosis can be further stratified into three ranges of percent blasts: < 5%, 5-20% and > 20%-30%.⁽⁸⁾ Even in the range of 5-20% blasts, there is a difference in prognosis. In one study, the median survival was 16 months in 100 patients with a blast cell percentage of 5-10% compared to a median survival of 5 months in 58 patients with a blast cell percentage of 11-20%.⁽⁹⁷⁾ A difference in prognosis has been noted even between patients with RA and < 3% bone marrow blasts compared to patients with RA and ≥3% (but < 5%) bone marrow blasts.⁽⁵²⁾

Besides the range of percent blasts, the type of blasts may have prognostic significance; patients with type III blasts may have a worse prognosis.⁽³⁹⁾ The type of blast can be defined as follows:

Type I: Undifferentiated progenitor cells in association with granulocytic colonies (promyelocytes, myelocytes, metamyelocytes, etc.). These cells resemble promyelocytes but have a very uncondensed (“reticular”) nuclear chromatin pattern. There are at least one and usually two or three prominent nucleoli, and slightly to moderately basophilic cytoplasm *without* a Golgi zone. Cytoplasmic granules are always absent and there are no Auer rods.⁽⁹⁾

Type II: The distinguishing feature from Type I is that a few primary (azurophilic) granules are present. The nuclear/cytoplasmic ratio tends to be lower. This type was established by the FAB group because the underlying dysplastic process leading to nuclear:cytoplasmic dissociation with subsequent hypogranulation (and occasionally

hypergranulation) often makes it difficult to distinguish between blasts and promyelocytes

Type III: Blasts with 20 or more azurophilic granules without a Golgi zone. This type was proposed by Goasguen and Bennett⁽³⁹⁾ because of the observation that there are cells with features of myeloblasts lacking a Golgi zone but with increased granules (≥ 6) as seen in promyelocytes and in abnormal promyelocytes (FAB M3).

The French-American-British Classification of MDS

Refractory cytopenia (anemia) (without increase in ringed sideroblasts, RA)

Historically, the starting point clinically for inclusion in this subgroup is anemia (hemoglobin < 11 g/dl) with a low reticulocyte count, though marked reticulocytosis in the range of 30% has been reported on the basis of maturational delay.⁽²⁶⁾

In this review, we would like to forward a better, less inclusive, more clinically applicable term than RA-refractory cytopenia as the anemia is often accompanied by thrombocytopenia and/or neutropenia (usually $< 140 \times 10^9/L$ and/or $< 4.0 \times 10^9/L$).⁽⁵⁷⁾ Furthermore, as mentioned previously, occasionally the neutropenia or thrombocytopenia can be isolated, i.e., without associated anemia. This category is clearly one of exclusion: blast cells should be $< 1\%$ in the peripheral blood and $< 5\%$ in the bone marrow, peripheral blood monocytes $< 1 \times 10^9/L$ and ringed sideroblasts should be $< 15\%$. The bone marrow is typically hypercellular with moderate to marked dyserythropoiesis alone or accompanied by dysgranulopoiesis/dysmegakaryopoiesis. Occasionally, there can be erythroid hypoplasia⁽¹⁹⁾; in rare cases, this can be to the extreme of red cell aplasia.⁽¹²⁸⁾

Refractory anemia with ringed sideroblasts

The morphological features described in RA are similar in this subgroup with the defining difference, of course, being a percentage of ringed sideroblasts $> 15\%$. The need for an adequate bone marrow aspirate must be emphasized as the iron stain of the core biopsy can be falsely negative because iron leaches out during the decalcification step.⁽³⁰⁾ Compared to RA(C), there is also less associated dysgranulopoiesis/megakaryopoiesis. In RARS in particular, a dimorphic population of red cells is noted in the peripheral blood attributed to deficient hemoglobinization in the clonal erythroid population. The percentage of bone marrow blast cells must be $< 5\%$; cases of $> 15\%$ ringed sideroblasts but $> 5\%$ blasts or monocytosis should be classified in the remaining subgroups. Not surprisingly, such patients have a worse prognosis in terms of overall survival and leukemic progression.⁽²⁸⁾

Refractory anemia with excess of blasts

The defining feature of this subgroup is an increase in bone marrow blasts $\geq 5\%$ but $\leq 20\%$ (with peripheral blood blasts $< 5\%$). Dysgranulopoiesis, particularly in terms of hypogranulation and hyposegmentation, is more pronounced than in the subgroups discussed previously as dysplasia in the other lineages. It also follows that, compared to the first two subgroups already discussed, patients with RAEB have a greater rate of progression to overt, acute leukemia than patients with RA or RARS (Table 2).

Furthermore, the inclusion of Type III blasts can change the diagnosis, particularly from RAEB to RAEB-T.⁽³⁹⁾

Table 2. Summary of morphologic features by FAB Classification*

FAB type of	Frequency	BM Blasts	Ringed Sideroblasts	Monocytes	Degree of Dyspoiesis
RA	35%	< 5 %*	< 15%	rare	+
RARS	20%	< 5%	> 15%*	rare	+
RAEB	0%	>5% >20%*	variable	rare	++
CMML	15%	1-20%	variable		Increased*
RAEB-T	15%	21%-30%*	variable	variable	

*characteristic features that help distinguish the subgroups

Table 3. Prognosis by FAB.

Studies	Varella ¹²¹	Mufti ⁷⁹	Goasguen ⁴⁰
# patients:	53	141	503
FAB Type: ^a			
RARS	53/ 12%	76/ 5%	45/ 3%
RA	38/ 15%	32/ 11%	32/ 8%
CMML	17/ 33%	22/ 13%	15/ 23%
RAEB	13/ 41%	11/ 28%	19/ 20%
RAEB-T	3/ 75%	5/ 55%	11/ 53%
Third MIC ³	Maschek ⁷¹		
1081	569		
51/ 8%	42/4%		
50/12%	27/16%		
11/ 14%	13/49%		
11/ 44%	9/42%		
5/ 60%	5/59%		

a median survival (mos)/% leukemic progression

Chronic myelomonocytic leukemia

The defining feature of chronic myelomonocytic leukemia (CMML) from the other four subgroups is an absolute peripheral blood monocytosis of $> 1 \times 10^9/L$. On the other hand, like the other subgroups, this entity shares many of the morphological features of MDS in terms of trilineage dyspoiesis as well as similar non-random chromosomal abnormalities. The degree of trilineage dysplasia can be variable and actually appears to be less severe the higher the peripheral blood neutrophil and monocyte counts.⁽¹⁰⁴⁾ There is often an increase in mature granulocytes but there can be a leftward shift in maturation, with the bone marrow occasionally resembling RAEB with 5-20% blasts. However, the percentage of marrow blasts is usually $< 5\%$. The monocytes can exhibit several dysplastic features: hyperlobulation, cytoplasmic granules or increased basophilia. Also, marked dysplasia can lead one to erroneously classify such cells as blasts.⁽³⁰⁾ Interestingly, the more immature monocytes - promonocytes - are more evident in the peripheral blood than in the marrow.⁽⁴⁹⁾

Unlike the other FAB subgroups, CMML can have certain peculiar clinical features that also seem to distinguish it from the other FAB subgroups - a tendency to develop serous effusions and tissue infiltration, particularly of the skin, liver, spleen and gingiva, and increased incidence of autoimmune phenomena ranging from polymyalgia rheumatica to cutaneous vasculitis.⁽⁶⁴⁾ These peculiar features have, in part, led some to consider CMML as an entity separate from the MDS.⁽⁷⁶⁾ Furthermore, over time, there have been several other inadequacies noted with the inclusion of CMML as part of MDS:

1. The poor prognostic power of this subgroup as evidenced by a very wide survival range of 11 to greater than 60 months in 175 patients compiled from 11 studies.⁽³⁾ This inadequacy can be rectified to some degree by stratifying the prognosis in terms of excess blasts ($> 5\%$) and peripheral monocytes ($> 3 \times 10^9/L$ absolute).^(32,107) In general, if there are $< 5\%$ blasts the survival is similar to RA or RARS (50 months) while if there are $> 5\%$ (but $< 20\%$) blasts, the survival is similar to RAEB.⁽¹⁰⁷⁾ In a study by Worsley et al, the survival was also similar to RAEB if the absolute peripheral blood monocyte count exceeded $2.6 \times 10^9/L$.⁽¹³²⁾

2. A second inadequacy has been the difficulty in clearly distinguishing CMML from the chronic myeloproliferative syndromes. This is because the clinical presentation can be identical: hepatosplenomegaly, leukocytosis and occasionally marrow fibrosis.⁽¹⁰⁹⁾ Furthermore, patients with chronic myeloid leukemia (CML) can have monocytosis ($> 1 \times 10^9/L$). But in CML there is generally less dysplasia, more immature leukocytes and a higher leukocyte count.⁽⁵⁸⁾ Obviously, difficulty arises in those cases lacking the Philadelphia chromosome. Those cases can then be further classified on the basis of whether they have rearrangement within the major breakpoint cluster region (*m-bcr*). The *m-bcr* positive (*m-bcr+*) patients resemble the Philadelphia chromosome + (Ph+) patients, therefore being essentially the same disease. The *m-bcr* negative (*m-bcr-*) patients have less leukocytosis, basophilia and immature myeloid precursors in the peripheral blood than the CML Ph+/*m-bcr+* or Ph-/*m-bcr+* cases. Within this group of Ph-/*m-bcr-* cases, a distinction can be made of those cases that fit the FAB criteria for CMML and those cases with a higher percentage of peripheral blood immature granulocytes (10-20% compared to $\leq 10\%$) and higher over-all white blood cell count (usually $> 13 \times 10^9/L$). However, these cases are related to CMML as it turns out that

these cases have similar chromosomal abnormalities as noted in CMML. These cases have been termed atypical CML.⁽⁷⁰⁾ The French-American-British group has recently distinguished between CML, aCML, and CMML on the basis of five predictive parameters: percent basophils, percent immature granulocytes, percent bone marrow erythroid precursors, percent monocytes, and degree of granulocyte dysplasia (Table 4).⁽⁷⁾

Table 4. Distinguishing features between CML, aCML, and CMML.

	CML	aCML	CMML
Peripheral Blood Basophilia (>2%)	> 2%*	< 2%	< 2%
Peripheral Blood Immature Granulocytes	> 20%*		10-20%* <10%
Dysgranulopoiesis	-	++*	+
Peripheral Blood Monocytes 10%*	< 3%	>3-10%	>
Increased Bone Marrow Erythroid Precursors	-	-	+*

***distinguishing features**

Refractory Anemia with excess blasts in transformation

Inclusion into this subgroup is based on one or more of the following features:

- A percent of bone marrow blasts of 21-30%
- $\geq 5\%$ peripheral blood blasts (with or without $> 21-30\%$ bone marrow blasts)
- Granulocyte precursors with Auer rods even if the percent bone marrow blasts is $< 20\%$. The latter situation was first described by Weisdorf et al.⁽¹²⁵⁾ These cases were included in RAEB-T because they were not associated with immediate progression to AML. A study by Scoazec et al supported this.⁽⁹⁹⁾ However, inclusion of these cases has recently been questioned⁽¹²⁴⁾ because of a study from M.D. Anderson, where patients classified as RAEB-T solely on the basis of Auer rods (n=29) had a median survival 41 weeks longer than the other RAEB-T patients (n = 179).⁽¹⁰²⁾

Lastly, regarding this subgroup, since patients under the age of 50 years may respond well to conventional chemotherapy for AML, it is reasonable to re-classify patients with RAEB-T under the age of 50 years as FAB M2.

Pathologic Variants of MDS

Therapy-related MDS

This probably involves a continuum of pancytopenia with dysplasia and < 5% marrow blasts, then MDS of the RAEB or RAEB-T subgroups, then overt AML.⁽⁶⁾ This temporal sequence is typical for the alkylating agents, while the epipodophyllotoxins typically “skip” the first two phases and present suddenly with AML. Generally, only a fifth to a half of therapy-related MDS cases can be readily classified by the FAB proposals, though the epipodophyllotoxins appear to be more easily classifiable by the FAB criteria and typically lack dysplasia.^(6,11,77) Two major factors making classification difficult are that there is no predominant cell type that is dysplastic and the marrow aspirate is often inadequate to review for dysplasia as the marrow is often hypocellular with fibrosis. As such, it is often difficult to clearly identify blasts. Ringed sideroblasts are common, however.

In the face of inadequate marrow aspiration, core biopsy in suspected cases of therapy-related MDS is very important. Besides revealing fibrosis, other features noted by the biopsy that support the diagnosis of t-MDS as well as confer a poor prognosis are the presence of ALIP and positivity for CD34 by immunostaining.

2. AML with trilineage dysplasia

Dysplasia involving one or several lineages is not uncommon in cases of *de novo* AML.^(13,29,41,61) Unlike the diagnosis of primary MDS where at least 10% of the cells of the respective lineage being considered should be dysplastic, the cut-off is more restrictive at > 50%. Dyserythropoiesis does not appear to correlate with lower remission rate than “normals,” unlike dysgranulopoiesis⁽⁴¹⁾ and probably dysmegakaryopoiesis.⁽⁶¹⁾ About 10-15% of cases will have trilineage dysplasia. These cases are more resistant to successful induction-remission therapy than cases of *de novo* AML without trilineage dysplasia; the complete remission rate is 20% lower, though most studies have not shown a negative impact on overall survival.^(13,29,41) It is unclear whether cases of AML with trilineage dysplasia represent acute transformation of clinically occult MDS or are a subtype of *de novo* AML. However, the former appears to be the case in those patients presenting with *de novo* AML with trilineage dysplasia and a history of occupational exposure.⁽²¹⁾ In a study by Cuneo et al of 70 adults with *de novo* AML, 43% were determined to have an occupational history. Those cases were associated with trilineage dysplasia, CD34 positivity and chromosomal abnormalities characteristic of therapy-related MDS/AML.⁽²¹⁾

Lastly, the presence of trilineage dysplasia after successful remission-induction therapy for *de novo* AML probably portends a higher risk of relapse.⁽⁸¹⁾

Human Immunodeficiency Virus (HIV)-related MDS

Unlike primary MDS, there is no obvious increase in transformation to AML.⁽⁴⁶⁾ However, like primary MDS, the presentation is usually one of cytopenia, the bone marrow cellularity is usually increased, and occasionally, like primary MDS, the marrow can be hypocellular. Increased marrow plasmacytosis and increased iron deposition (without ringed sideroblasts) are present.⁽³⁰⁾ On bone marrow biopsy, lymphoid

aggregates, serous atrophy, granulomas and fibrosis can be noted.⁽⁵⁹⁾ The latter two clinically correlate with infection, particularly mycobacterial or *Pneumocystis*.⁽⁵⁹⁾

In a review of 216 bone marrow biopsies/aspirates and/or imprint preparations, Karcher and Frost⁽⁵⁹⁾ noted dysplastic features of at least one lineage in 70% of the patients. Dyserythropoiesis was noted in half of the patients: multinucleation, nuclear irregularity and internuclear chromatin bridge formation. Next most common was dysmegakaryopoiesis, noted in a third of the patients: micromegakaryocytes, nuclear hyposegmentation and nuclear fragmentation. Least common was dysgranulopoiesis, noted in about a fifth of patients: mild nuclear:cytoplasmic dissociation, multinucleation, and hypogranularity.

There is clearly more than one mechanism responsible for myelodysplasia in HIV disease: concomitant infections (opportunistic and/or possibly HIV) particularly since myelodysplasia correlates with the stage of HIV infection,⁽⁵⁶⁾ nutritional factors, autoimmunity and drug effects. Regarding the latter, Harris et al⁽⁴⁶⁾ found dyserythropoiesis in all patients on azothymidine (AZT) with dysplasia besides the megaloblastosis, which is well described with AZT. Regarding the role of infection, a recent study showed morphological similarities of the bone marrow of HIV-positive patients with those of HIV-negative patients with infectious disease but not with patients with primary MDS.⁽⁵⁶⁾

MDS with Myelofibrosis (“Hyperfibrotic MDS”)

Fibrosis, defined as a focal or diffuse increase in the number and thickness of the reticulin fibers, can be noted in approximately half of the cases of MDS. In these cases, the degree of fibrosis is mild to moderate. But there now have been several studies of MDS patients (approximately 100 cases) with marked fibrosis, which can be termed “hyperfibrotic MDS.”^(66,71,86,105,123,125) These cases are usually characterized pathologically by the striking increase in fibrosis as well as frequent/increased micromegakaryocytes. The megakaryocytes may be hypolobated or the nuclei may be fragmented.⁽⁵¹⁾ The clinical course is marked by a shorter survival than usual in cases of MDS; a median survival more similar to RAEB than RA or RARS.^(66,71,86,105,123,125) Despite the poor prognosis of “hyperfibrotic MDS,” there is a provocative report of three such patients entering a hematological remission after prednisolone.⁽¹²⁵⁾

The peripheral blood finding of leukoerythroblastosis and tear drop cells coupled with the increased megakaryocytes (with consequent production of various cytokines such as platelet-derived growth factor that can lead to fibrosis^(27,51)) has led to speculation that “hyperfibrotic” MDS is actually a myeloproliferative syndrome.⁽²⁶⁾ Actually, in some cases, there is hepatosplenomegaly with ferrokinetic studies supportive of extramedullary hematopoiesis.⁽⁹²⁾ This has led Reilly and Dolan⁽⁹¹⁾ to suggest the term “transitional myelodysplasia-myelofibrosis,” which may straddle several entities⁽⁵¹⁾:

- “hyperfibrotic” MDS - as described above, with trilineage dysplasia, absent hepatosplenomegaly, bone marrow blasts are moderately increased in the 10-20% range.

- “acute myelosclerosis” - rapidly fatal course with more pronounced fibrosis than “hyperfibrotic MDS” but like “hyperfibrotic MDS,” hepatosplenomegaly is typically absent.
- AML, M7 (“acute megakaryoblastic leukemia”) - defining feature compared to the two above entities is, of course, a blast population > 30% with immunostaining demonstrating the blasts to be megakaryocytic.⁽¹⁰⁾
- myeloid metaplasia with myelofibrosis - trilineage bone marrow dysplasia is lacking, while moderate to marked splenomegaly helps separate this entity further from “hyperfibrotic” MDS.

Hypoplastic MDS

About 10-15% of MDS bone marrows are hypocellular^(73,113) defined as a cellularity less than 25-30% and < 20% in patients over the age of 60.⁽¹¹⁷⁾ It also appears to be more common a finding in MDS than in AML.⁽¹¹⁸⁾ Cases of hypocellular AML can be confused with hypocellular MDS.⁽⁵⁰⁾ Rarely is the hypocellularity less than 10% as noted in aplastic anemia.⁽³³⁾ Distinguishing features of hypocellular MDS from aplastic anemia may be the presence of (i) ALIP, (ii) islands of erythroid precursors, or (iii) dysmegakaryopoiesis and megakaryoblasts as demonstrated by immunostaining.⁽³⁸⁾ Whether hypocellularity confers a poor prognosis is unclear; some studies show a worse prognosis,^(83,94) while more recent studies show no negative impact.^(113,119,133)

“Early” MDS

Finally, what about cases lacking overt dysplasia in which all of the above disorders as well as the various medical conditions associated with dysplasia have been excluded but there persists an unexplainable abnormality in the peripheral blood such as a macrocytosis without anemia or monocytosis? These are cases that Dr. Terry Hamblin has referred to perhaps tongue in cheek as NYMDS (not yet MDS) or NQMDS (not quite MDS).⁽⁴⁴⁾ Recently, Antilla et al studied a group of elderly patients with macrocytic anemia that did not fulfill the FAB criteria for MDS. Four molecular markers for indirect/direct evidence of clonality were applied - DNA hypermethylation at the calcitonin A gene-5' area, N-RAS point mutations at codon 12 and 13, in vitro colony formation of peripheral blood progenitor cells and cytogenetics of the bone marrow cells. In 8/9 of these cases that did not fulfill the FAB criteria for MDS, at least one molecular study was abnormal as such, consistent with an early stage of MDS. It thus seems that in cases without overt dysplastic morphology, the demonstration of a clonal cytogenetic abnormality or monoclonality by other methods⁽⁴⁾ could conceivably lead to a provisional diagnosis of MDS.

Prognosis

In addition to the percentage of blasts, which has prognostic importance, the presence of bi- and tricytopenias, age, sex, and chromosomal abnormalities provide additional information that can assist in predicting leukemic evolution and survival. Several scoring systems have evolved over the years. All of these systems have developed three survival curves that have median survivals of approximately 60, 30, and 15 months. Recently, an international group has evaluated 758 patients with untreated MDS from

seven large centers (ASH Abstract #1065, Blood: 86, 270a, 1995). By combining the percentage of blasts, cytopenias, and cytogenetics, four survival curves can be generated. Cytogenetic subgroups with good outcome included normal, -Y, del(20q) and 5q-. Poor outcome cytogenetics included abnormalities of chromosome 7 or complex (two or more). Based on multivariate analyses, there were four groups with median survival of 5.7, 3.4, 1.2, and .42 years. Under age 60 years improved the survival of the two best groups considerably. A simple scoring system will enable an investigator to determine the survival, leukemic evolution and likelihood of long-term survival very accurately.

Bibliography

1. Acin P, Florensa L, Andreu LL, Woessner S: Cytoplasmic abnormalities of erythroblasts as a marker for ringed sideroblasts in myelodysplastic syndromes [letter]. *European Journal of Haematology* 54:276, 1995
2. Amenomori T, Tomonaga M, Jinnai I, Soda H, Nonaka H, Matsuo T, Yoshida Y, Kuriyama K, Ichimaru M, Suematsu T: Cytogenetic and cytochemical studies on progenitor cells of primary acquired sideroblastic anemia (PASA): involvement of multipotent myeloid stem cells in PASA clone and mosaicism with normal clone. *Blood* 70:1367, 1987
3. Anonymous: Recommendations for a morphologic, immunologic, and cytogenetic (MIC) working classification of the primary and therapy-related myelodysplastic disorders. Report of the workshop held in Scottsdale, Arizona, USA, on February 23-25, 1987. Third MIC Cooperative Study Group. *Cancer Gen & Cytogenet* 32:1, 1988
4. Anttila P, Ihalainen J, Salo A, Heiskanen M, Juvonen E, Palotie A: Idiopathic macrocytic anaemia in the aged: molecular and cytogenetic findings. *Br J Haematol* 90:797, 1995
5. Bartl R, Frisch B, Baumgart R: Morphologic classification of the myelodysplastic syndromes (MDS): combined utilization of bone marrow aspirates and trephine biopsies. *Leukemia Res* 16:15, 1992
6. Bennett JM: Secondary acute myeloid leukemia [editorial]. *Leukemia Res* 19:231, 1995
7. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick H, Sultan C, Cox C: The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Group [see comments]. *Br J Haematol* 87:746, 1994
8. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C: Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol* 33:451, 1976
9. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C: Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 51:189, 1982

10. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C: Criteria for the diagnosis of acute leukemia of megakaryocyte lineage (M7). A report of the French-American-British Cooperative Group. *Ann Int Med* 103:460, 1985
11. Bennett JM, Moloney WC, Greene MH, Boice JD, Jr. Acute myeloid leukemia and other myelopathic disorders following treatment with alkylating agents. *Hematologic Pathol* 1:99, 1987
12. Block M, Jacobson LO, Bethard WF: Preleukemic human leukemia. *JAMA* 152:1018, 1953
13. Brito-Babapulle F, Catovsky D, Galton DA: Myelodysplastic relapse of de novo acute myeloid leukaemia with trilineage myelodysplasia: a previously unrecognized correlation. *Br J Haematol* 68:411, 1988
14. Castello A, Coci A, Magrini U: Paraneoplastic marrow alterations in patients with cancer. *Haematologica* 77:392, 1992
15. Cazzola M, Barosi G, Gobbi PG, Invernizzi R, Riccardi A, Ascari E: Natural history of idiopathic refractory sideroblastic anemia. *Blood* 71:305, 1988
16. Clatch RJ, Krigman HR, Peters MG, Zutter MM: Dysplastic haemopoiesis following orthotopic liver transplantation: comparison with similar changes in HIV infection and primary myelodysplasia. *Br J Haematol* 88:685, 1994
17. Coiffier B, Adeleine P, Gentilhomme O, Felman P, Treille-Ritouet D, Bryon PA: Myelodysplastic syndromes. A multiparametric study of prognostic factors in 336 patients. *Cancer* 60:3029, 1987
18. Colon-Otero G, Menke D, Hook CC: A practical approach to the differential diagnosis and evaluation of the adult patient with macrocytic anemia. [Review]. *Med Clin N Amer* 76:581, 1992
19. Cook MK: Red cell hypoplasia associated with myeloproliferative and myelodysplastic syndrome [letter; comment]. *J Clin Pathol* 42:890, 1989
20. Cuneo A, Fagioli F, Pazzi I, Tallarico A, Previati R, Piva N, Carli MG, Balboni M, Castoldi G: Morphologic, immunologic and cytogenetic studies in acute myeloid leukemia following occupational exposure to pesticides and organic solvents. *Leukemia Res* 16:789, 1992
21. Cuneo A, Van Orshoven A, Michaux JL, Boogaerts M, Louwagie A, Doyen C, Dal Cin P, Fagioli F, Castoldi G, Van den Berghe H: Morphologic, immunologic and cytogenetic studies in erythroleukaemia: evidence for multilineage involvement and identification of two distinct cytogenetic- clinicopathological types. *Br J Haematol* 75:346, 1990
22. Dacie JV, Smith MD, White JC, Mollin DL: Refractory normoblastic anaemia: A clinical and haematological study of seven cases. *Br J Haematol* 5:56, 1995
23. Davey FR, Erber WN, Gatter KC, Mason DY: Abnormal neutrophils in acute myeloid leukemia and myelodysplastic syndrome. *Hum Pathol* 19:454, 1988
24. de Bock R, de Jonge M, Korthout M, Wouters E, van Bockstaele D, van der Planken M, Peetermans M: Hypoplastic acute leukemia: description of eight cases and search for hematopoietic inhibiting activity. *Ann Hematol* 65:247, 1992
25. Delacretaz F, Schmidt PM, Piguët D, Bachmann F, Costa J: Histopathology of myelodysplastic syndromes. The FAB classification (proposals) applied to bone marrow biopsy. *Amer J Clinl Path* 87:180, 1987

26. dePree C, Cabrol C, Frossard JL, Beris P: Pseudoreticulocytosis in a case of myelodysplastic syndrome with translocation t (1:14) (q42;q32). *Semin Hematol* 32:232, 1995
27. Dickstein JI, Vardiman JW: Issues in the pathology and diagnosis of the chronic myeloproliferative disorders and the myelodysplastic syndromes. [Review]. *Amer J Clin Path* 99:513, 1993
28. Economopoulos T, Karakassis D, Stathakis N, Pappa V, Raptis S: Significance of bone marrow sideroblastosis in myelodysplastic syndromes [letter]. *Eur J Haematol* 45:118, 1990
29. Estienne MH, Fenaux P, Preudhomme C, Lai JL, Zandecki M, Lepelley P, Cosson A: Prognostic value of dysmyelopoietic features in de novo acute myeloid leukaemia: a report on 132 patients. *Clin & Lab Haematol* 12:57, 1990
30. Farhi DC: Myelodysplastic syndromes and acute myeloid leukemia. Diagnostic criteria and pitfalls. [Review]. *Pathology Annual* 30:29, 1995
31. Felman P, Bryon PA, Gentilhomme O, Ffrench M, Charrin C, Espinouse D, Viala JJ: The syndrome of abnormal chromatin clumping in leucocytes: a myelodysplastic disorder with proliferative features? [see comments]. *Br J Haematol* 70:49, 1988
32. Fenaux P, Beuscart R, Lai JL, Jouet JP, Bauters F: Prognostic factors in adult chronic myelomonocytic leukemia: an analysis of 107 cases. *J Clin Oncol* 6:1417, 1988
33. Fohlmeister I, Fischer R, Modder B, Rister M, Schaefer HE: Aplastic anaemia and the hypocellular myelodysplastic syndrome: histomorphological, diagnostic, and prognostic features. *J Clin Path* 38:1218, 1985
34. Galton DA: The myelodysplastic syndromes. Part I. What are they? Part II. Classification. [Review]. *Scand J Haematol-Suppl* 45:11, 1986
35. Garand R, Gardais J, Bizet M, Bremond JL, Accard F, Callat MP, de Bouchony ET, Goasguen JE: Heterogeneity of acquired idiopathic sideroblastic anaemia (AISA). *Leukemia Res* 16:463, 1992
36. Gattermann N, Aul C, Schneider W: Risk of leukemic transformation in two types of acquired idiopathic sideroblastic anemia. *Hamatologie und Bluttransfusion* 33:374, 1990
37. Gerrard JM, McNicol A: Platelet storage pool deficiency, leukemia, and myelodysplastic syndromes. [Review]. *Leukemia & Lymphoma* 8:277, 1992
38. Goasguen JE, Bennett JM: Classification and morphologic features of the myelodysplastic syndromes. [Review]. *Semin Oncol* 19:4, 1992
39. Goasguen JE, Bennett JM, Cox C, Hambley H, Mufti G, Flandrin G: Prognostic implication and characterization of the blast cell population in the myelodysplastic syndrome. *Leukemia Res* 15:1159, 1991
40. Goasguen JE, Garand R, Bizet M, Bremond JL, Gardais J, Callat MP, Accard F, Chaperon J: Prognostic factors of myelodysplastic syndromes—A simplified 3-D scoring system. *Leukemia Res* 14:255, 1990
41. Goasguen JE, Matsuo T, Cox C, Bennett JM: Evaluation of the dysmyelopoiesis in 336 patients with de novo acute myeloid leukemia: major importance of dysgranulopoiesis for remission and survival. *Leukemia* 6:520, 1992

42. Guyotat D, Campos L, Thomas X, Vila L, Shi ZH, Charrin C, Gentilhomme O, Fiere D: Myelodysplastic syndromes: a study of surface markers and in vitro growth patterns. *Am J Hematol* 34:26, 1990
43. Hadnagy C, Laszlo GA: Acquired dyserythropoiesis in liver disease. *Br J Haematol* 78:283, 1991
44. Hamblin T: Minimal diagnostic criteria for the myelodysplastic syndrome in clinical practice. *Leukemia Res* 16:3, 1992
45. Hamilton-Patterson JL: Preleukemic anaemia. *Acta Haematologica* 2:309, 1949
46. Harris CE, Biggs JC, Concannon AJ, Dodds AJ: Peripheral blood and bone marrow findings in patients with acquired immune deficiency syndrome. *Pathology* 22:206, 1990
47. Hast R: Sideroblasts in myelodysplasia: their nature and clinical significance. [Review]. *Scand J Haematol-Suppl* 45:53, 1986
48. Head DR, Kopecky K, Bennett JM, Grenier K, Morrison FS, Miller KB, Grever MR: Pathogenetic implications of internuclear bridging in myelodysplastic syndrome. An Eastern Cooperative Oncology Group/Southwest Oncology Group Cooperative Study. *Cancer* 64:2199, 1989
49. Ho PJ, Gibson J, Vincent P, Joshua D: The myelodysplastic syndromes: diagnostic criteria and laboratory evaluation. [Review]. *Pathology* 25:297, 1993
50. Howe RB, Bloomfield CD, McKenna RW: Hypocellular acute leukemia. *Am J Med* 72:391, 1982
51. Imbert M, Nguyen D, Sultan C: Myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML) with myelofibrosis. [Review]. *Leukemia Res* 16:51, 1992
52. Iwabuchi A, Ohyashiki K, Ohyashiki JH, Kimura Y, Lin KY, Aizawa S, Nehashi Y, Miyazawa K, Yaguchi M, Toyama K: Percentages of bone marrow blasts and chromosomal changes in patients with refractory anemia help to determine prognoses. *Int J Hematol* 60:207, 1994
53. Jaen A, Irriguible D, Milla F, Vallespi T, Torradadella M, Abella E, Lafuente R, Woessner S: Abnormal chromatin clumping in leucocytes: a clue to a new subtype of myelodysplastic syndrome. *Eur J Haematol* 45:209, 1990
54. Jensen IM, Hokland P: The proliferative activity of myelopoiesis in myelodysplasia evaluated by multiparameter flow cytometry. *Br J Haematol* 87:477, 1994
55. Juneja SK, Imbert M, Jouault H, Scoazec JY, Sigaux F, Sultan C: Haematological features of primary myelodysplastic syndromes (PMDS) at initial presentation: a study of 118 cases. *J Clin Path* 36:1129, 1983
56. Kaloutsi V, Kohlmeyer U, Maschek H, Nafe R, Choritz H, Amor A, Georgii A: Comparison of bone marrow and hematologic findings in patients with human immunodeficiency virus infection and those with myelodysplastic syndromes and infectious diseases. *Am J Clin Path* 101:123, 1994
57. Kampmeier P, Anastasi J, Vardiman JW: Issues in the pathology of the myelodysplastic syndromes. [Review]. *Hematol-Oncol Clin N Amer* 6:501, 1992
58. Kantarjian HM, Shtalrid M, Kurzrock R, Blick M, Dalton WT, LeMaistre A, Stass SA, McCredie KB, Gutterman J, Freireich EJ, et al: Significance and correlations of molecular analysis results in patients with Philadelphia chromosome-negative chronic

- myelogenous leukemia and chronic myelomonocytic leukemia. *Am J Med* 85:639, 1988
59. Karcher DS, Frost AR: The bone marrow in human immunodeficiency virus (HIV)-related disease. Morphology and clinical correlation. *Am J Clin Path* 95:63, 1991
 60. Kawaguchi M, Nehashi Y, Aizawa S, Toyama K: Comparative study of immunocytochemical staining versus Giemsa stain for detecting dysmegakaryopoiesis in myelodysplastic syndromes (MDS) [published erratum appears in *Eur J Haematol* 1990 Aug;45(2):125]. *Eur J Haematol* 44:89, 1990
 61. Kobayashi S, Seki K, Katayama N, Akiba C, Yamamoto T, Sakai K, Yamaguchi M, Maruta A, Noguchi T, Ogawa K, et al: [Clinical significance of micromegakaryocytes in de novo AML]. [Japanese]. *Rinsho Ketsueki - Japanese J Clin Hematol* 34:313, 1993
 62. Kouides PA, Bennett JM: Morphology and classification of myelodysplastic syndromes. [Review]. *Hematol-Oncol Clin N Amer* 6:485, 1992
 63. Kouides PA, Bennett JM: Transformation of chronic myelomonocytic leukemia to acute lymphoblastic leukemia: case report and review of the literature of lymphoblastic transformation of myelodysplastic syndrome. [Review]. *Am J Hematol* 49:157, 1995
 64. Kouides PA, Bennett JM: Myelodysplastic Syndromes, in Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE (eds): *Clinical Oncology*, New York, Churchill Livingstone, 1995, p 1977
 65. Kuriyama K, Tomonaga M, Matsuo T, Ginnai I, Ichimaru M: Diagnostic significance of detecting pseudo-Pelger-Hu't anomalies and micro-megakaryocytes in myelodysplastic syndrome. *Br J Haematol* 63:665, 1986
 66. Lambertenghi-Delilieri G, Orazi A, Luksch R, Annaloro C, Soligo D: Myelodysplastic syndrome with increased marrow fibrosis: a distinct clinico-pathological entity [see comments]. *Br J Haematol* 78:161, 1991
 67. Langenhuijsen MM: Neutrophils with ring-shaped nuclei in myeloproliferative disease. *Br J Haematol* 58:227, 1984
 68. List AF, Spier CM, Cline A, Doll DC, Garewal H, Morgan R, Sandberg AA: Expression of the multidrug resistance gene product (P-glycoprotein) in myelodysplasia is associated with a stem cell phenotype. *Br J Haematol* 78:28, 1991
 69. Mangi MH, Salisbury JR, Mufti GJ: Abnormal localization of immature precursors (ALIP) in the bone marrow of myelodysplastic syndromes: current state of knowledge and future directions. [Review]. *Leukemia Res* 15:627, 1991
 70. Martiat P, Michaux JL, Rodhain J: Philadelphia-negative (Ph-) chronic myeloid leukemia (CML): comparison with Ph+ CML and chronic myelomonocytic leukemia. The Groupe Francais de Cytogenetique Hematologique. *Blood* 78:205, 1991
 71. Maschek H, Georgii A, Kaloutsi V, Werner M, Bandekar K, Kressel MG, Choritz H, Freund M, Hufnagl D: Myelofibrosis in primary myelodysplastic syndromes: a retrospective study of 352 patients. *Eur J Haematol* 48:208, 1992
 72. Maschek H, Gutzmer R, Choritz H, Georgii A: Life expectancy in primary myelodysplastic syndromes: a prognostic score based upon histopathology from bone marrow biopsies of 569 patients. *Eur J Haematol* 53:280, 1994

73. Maschek H, Kaloutsi V, Rodriguez-Kaiser M, Werner M, Choritz H, Mainzer K, Dietzfelbinger M, Georgii A: Hypoplastic myelodysplastic syndrome: incidence, morphology, cytogenetics, and prognosis. *Ann Hematol* 66:117, 1993
74. Mathew P, Tefferi A, Dewald GW, Goldberg SL, Su J, Hoagland HC, Noel P: The 5q- syndrome: a single-institution study of 43 consecutive patients. *Blood* 81:1040, 1993
75. Menke DM, Colon-Otero G, Cockerill KJ, Jenkins RB, Noel P, Pierre RV: Refractory thrombocytopenia. A myelodysplastic syndrome that may mimic immune thrombocytopenic purpura [see comments]. *Am J Clin Pathol* 98:502, 1992
76. Michaux JL, Martiat P: Chronic myelomonocytic leukaemia (CMML)Ña myelodysplastic or myeloproliferative syndrome? [Review]. *Leukemia & Lymphoma* 9:35, 1993
77. Michels SD, McKenna RW, Arthur DC, Brunning RD: Therapy-related acute myeloid leukemia and myelodysplastic syndrome: a clinical and morphologic study of 65 cases. *Blood* 65:1364, 1985
78. Min YH, Lee ST, Min DW, Kim TS, Lee CH, Lee BK, Hahn JS, Ko YW: CD34 immunohistochemical staining of bone marrow biopsies in myelodysplastic syndromes. *Yonsei Medical Journal* 36:1, 1995
79. Mori H, Niikura H, Terada H, Fujita K: [Morphological analysis of the megakaryocytes in myelodysplastic syndrome]. [Japanese]. *Rinsho Byori - Japanese J Clin Pathol* 38:1347, 1990
80. Mufti GJ, Stevens JR, Oscier DG, Hamblin TJ, Machin D: Myelodysplastic syndromes: a scoring system with prognostic significance. *Br J Haematol* 59:425, 1985
81. Nagai K, Matsuo T, Atogami S, Moriuchi Y, Yoshida Y, Kuriyama K, Tomonaga M: Remission with morphological myelodysplasia in de novo acute myeloid leukaemia: implications for early relapse. *Br J Haematol* 81:33, 1992
82. Najean Y, Lecompte T: Chronic pure thrombocytopenia in elderly patients. An aspect of the myelodysplastic syndrome. *Cancer* 64:2506, 1989
83. Nand S, Godwin JE: Hypoplastic myelodysplastic syndrome. *Cancer* 62:958, 1988
84. Oertel J, Oertel B, Beyer J, Huhn D: CD 34 immunotyping of blasts in myelodysplasia. *Ann Hematol* 68:77, 1994
85. Oguma S, Yoshida Y, Uchino H, Okuma M, Maekawa T, Nomura T: Infection in myelodysplastic syndromes before evolution into acute non-lymphoblastic leukemia. *Int J Hematol* 60:129, 1994
86. Ohyashiki K, Sasao I, Ohyashiki JH, Murakami T, Iwabuchi A, Tauchi T, Saito M, Nakazawa S, Serizawa H, Ebihara Y, et al: Clinical and cytogenetic characteristics of myelodysplastic syndromes developing myelofibrosis. *Cancer* 68:178, 1991
87. Orazi A, Cattoretti G, Soligo D, Luksch R, Lambertenghi-Delilieri G: Therapy-related myelodysplastic syndromes: FAB classification, bone marrow histology, and immunohistology in the prognostic assessment. *Leukemia* 7:838, 1993
88. Pagliuca A, Layton DM, Manoharan A, Gordon S, Green PJ, Mufti GJ: Myelofibrosis in primary myelodysplastic syndromes: a clinico-morphological study of 10 cases [see comments]. *Br J Haematol* 71:499, 1989

89. Pomeroy C, Oken MM, Rydell RE, Filice GA: Infection in the myelodysplastic syndromes. *Am J Med* 90:338, 1991
90. Raman BK, Van Slyck EJ, Riddle J, Sawdyk MA, Abraham JP, Saeed SM: Platelet function and structure in myeloproliferative disease, myelodysplastic syndrome, and secondary thrombocytosis. *Am J Clin Pathol* 91:647, 1989
91. Raza A, Gezer S, Mundle S, Gao XZ, Alvi S, Borok R, Rifkin S, Iftikhar A, Shetty V, Parcharidou A, et al: Apoptosis in bone marrow biopsy samples involving stromal and hematopoietic cells in 50 patients with myelodysplastic syndromes. *Blood* 86:268, 1995
92. Reilly JT, Dolan G: Proposed classification for the myelodysplasia/myelofibrosis syndromes [letter; comment]. *Br J Haematol* 79:653, 1991
93. Rezuke WN, Anderson C, Pastuszak WT, Conway SR, Firshein SI: Arsenic intoxication presenting as a myelodysplastic syndrome: a case report. *Am J Hematol* 36:291, 1991
94. Riccardi A, Giordano M, Girino M, Cazzola M, Montecucco CM, Cassano E, Danova M, Ucci G, Castello A, Coci A, et al: Refractory cytopenias: clinical course according to bone marrow cytology and cellularity. *Blut* 54:153, 1987
95. Rios A, Canizo MC, Sanz MA, Vallespi T, Sanz G, Torradabella M, Gomis F, Ruiz C, San Miguel JF: Bone marrow biopsy in myelodysplastic syndromes: morphological characteristics and contribution to the study of prognostic factors. *Br J Haematol* 75:26, 1990
96. Ruutu P: Granulocyte function in myelodysplastic syndromes. [Review]. *Scand J Haematol-Suppl* 45:66, 1986
97. Sanz GF, Sanz MA, Vallespi T, Canizo MC, Torradabella M, Garcia S, Irriguible D, San Miguel JF: 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* 74:395, 1989
98. Schumacher HR, Nand S: *Myelodysplastic Syndromes: Approach to Diagnosis and Treatment*. New York, Igaku-Shoin, 1995
99. Scoazec JY, Imbert M, Crofts M, Jouault H, Juneja SK, Vernant JP, Sultan C: Myelodysplastic syndrome or acute myeloid leukemia? A study of 28 cases presenting with borderline features. *Cancer* 55:2390, 1985
100. Scott CS, Cahill A, Bynoe AG, Ainley MJ, Hough D, Roberts BE: Esterase cytochemistry in primary myelodysplastic syndromes and megaloblastic anaemias: demonstration of abnormal staining patterns associated with dysmyelopoiesis. *Br J Haematol* 55:411, 1983
101. Seo IS, Li CY, Yam LT: Myelodysplastic syndrome: diagnostic implications of cytochemical and immunocytochemical studies. *Mayo Clinic Proceedings* 68:47, 1993
102. Seymour JF, Estey EH: The prognostic significance of auer rods in myelodysplasia [see comments]. *Br J Haematol* 85:67, 1993
103. Singh M, Bofinger A, Taylor K, Ba Pe R: Myelodysplasia with myelofibrosis—A distinct subgroup within the myelodysplastic syndromes. *Pathology* 26:69, 1994

104. Solal-Celigny P, Desaint B, Herrera A, Chastang C, Amar M, Vroclans M, Brousse N, Mancilla F, Renoux M, Bernard JF, et al: Chronic myelomonocytic leukemia according to FAB classification: analysis of 35 cases. *Blood* 63:634, 1984
105. Soligo DA, Oriani A, Annaloro C, Cortelezzi A, Calori R, Pozzoli E, Nosella D, Orazi A, Deliliers GL: CD34 immunohistochemistry of bone marrow biopsies: prognostic significance in primary myelodysplastic syndromes. *Am J Hematol* 46:9, 1994
106. Sonneveld P, van Dongen JJ, Hagemeijer A, van Lom K, Nooter K, Schoester M, Adriaansen HJ, Tsuruo T, de Leeuw K: High expression of the multidrug resistance P-glycoprotein in high-risk myelodysplasia is associated with immature phenotype. *Leukemia* 7:963, 1993
107. Storniolo AM, Moloney WC, Rosenthal DS, Cox C, Bennett JM: Chronic myelomonocytic leukemia. *Leukemia* 4:766, 1990
108. Takahashi M, Koike T, Nagayama R, Fujiwara M, Koyama S, Ohnishi M, Nakamori Y, Soga N, Aoki S, Tatewaki W, et al: Myelodysplastic syndrome with myelofibrosis: myelodysplastic syndrome as a major primary disorder for acute myelofibrosis. *Clin & Lab Haematol* 13:17, 1991
109. Tefferi A, Hoagland HC, Therneau TM, Pierre RV: Chronic myelomonocytic leukemia: natural history and prognostic determinants. *Mayo Clinic Proc* 64:1246, 1989
110. Tham KT, Cousar JB, Macon WR: Silver stain for ringed sideroblasts. A sensitive method that differs from Perls's reaction in mechanism and clinical application. *Am J Clin Pathol* 94:73, 1990
111. Thiede T, Engquist L, Billstrom R: Application of megakaryocytic morphology in diagnosing 5q-syndrome. *Eur J Haematol* 41:434, 1988
112. Thiele J, Quitmann H, Wagner S, Fischer R: Dysmegakaryopoiesis in myelodysplastic syndromes (MDS): an immunomorphometric study of bone marrow trephine biopsy specimens. *J Clin Pathol* 44:300, 1991
113. Toyama K, Ohyashiki K, Yoshida Y, Abe T, Asano S, Hirai H, Hirashima K, Hotta T, Kuramoto A, Kuriya S, et al: Clinical and cytogenetic findings of myelodysplastic syndromes showing hypocellular bone marrow or minimal dysplasia, in comparison with typical myelodysplastic syndromes. *Int J Hematol* 58:53, 1993
114. Treacy M, Lai L, Costello C, Clark A: Peripheral blood and bone marrow abnormalities in patients with HIV related disease. *Br J Haematol* 65:289, 1987
115. Tricot G, De Wolf-Peeters C, Hendrickx B, Verwilghen RL: Bone marrow histology in myelodysplastic syndromes. I. Histological findings in myelodysplastic syndromes and comparison with bone marrow smears. *Br J Haematol* 57:423, 1984
116. Tricot G, De Wolf-Peeters C, Vlietinck R, Verwilghen RL: Bone marrow histology in myelodysplastic syndromes. II. Prognostic value of abnormal localization of immature precursors in MDS. *Br J Haematol* 58:217, 1984
117. Tuzuner N, Bennett JM: Reference standards for bone marrow cellularity [letter]. *Leukemia Res* 18:645, 1994
118. Tuzuner N, Cox C, Rowe JM, Bennett JM: Bone marrow cellularity in myeloid stem cell disorders: impact of age correction. *Leukemia Res* 18:559, 1994

119. Tuzuner N, Cox C, Rowe JM, Watrous D, Bennett JM: Hypocellular myelodysplastic syndromes (MDS): new proposals. *Br J Haematol* 91:612, 1995
120. Van den Berghe H: The 5q- syndrome. *Scand J Haematol-Suppl* 45:78, 1986
121. Vandermolen L, Rice L, Rose MA, Lynch EC: Ringed sideroblasts in primary myelodysplasia. Leukemic propensity and prognostic factors. *Arch Int Med* 148:653, 1988
122. Varela BL, Chuang C, Woll JE, Bennett JM: Modifications in the classification of primary myelodysplastic syndromes: the addition of a scoring system. *Hematological Oncology* 3:55, 1985
123. Verhoef GE, De Wolf-Peeters C, Ferrant A, Deprez S, Meeus P, Stul M, Zachee P, Cassiman JJ, Van den Berghe H, Boogaerts MA: Myelodysplastic syndromes with bone marrow fibrosis: a myelodysplastic disorder with proliferative features. *Ann Hematol* 63:235, 1991
124. Verhoef GE, Pittaluga S, De Wolf-Peeters C, Boogaerts MA: FAB classification of myelodysplastic syndromes: merits and controversies. [Review]. *Ann Hematol* 71:3, 1995
125. Watts EJ, Majer RV, Green PJ, Mavor WO: Hyperfibrotic myelodysplasia: a report of three cases showing haematological remission following treatment with prednisolone [see comments]. *Br J Haematol* 78:120, 1991
126. Weisdorf DJ, Oken MM, Johnson GJ, Rydell RE: Auer rod positive dysmyelopoietic syndrome. *Am J Hematol* 11:397, 1981
127. Widell S, Hellstrom-Lindberg E, Kock Y, Lindberg M, Ost A, Hast R: Peripheral blood neutrophil morphology reflects bone marrow dysplasia in myelodysplastic syndromes. *Am J Hematol* 49:115, 1995
128. Williamson PJ, Oscier DG, Bell AJ, Hamblin TJ: Red cell aplasia in myelodysplastic syndrome [see comments]. *J Clin Pathol* 44:431, 1991
129. Winfield DA, Polaczar SV: Bone marrow histology. 3: Value of bone marrow core biopsy in acute leukaemia, myelodysplastic syndromes, and chronic myeloid leukaemia [see comments]. [Review]. *J Clin Pathol* 45:855, 1992
130. Wong KF, Chan JK: Are ÔdysplasticÕ and hypogranular megakaryocytes specific markers for myelodysplastic syndrome? *Br J Haematol* 77:509, 1991
131. Woodlock TJ, Seshi B, Sham RL, Cyran EM, Bennett JM: Use of cell surface antigen phenotype in guiding therapeutic decisions in chronic myelomonocytic leukemia. *Leukemia Res* 18:173, 1994
132. Worsley A, Oscier DG, Stevens J, Darlow S, Figs A, Mufti GJ, Hamblin TJ: Prognostic features of chronic myelomonocytic leukaemia: a modified Bournemouth score gives the best prediction of survival. *Br J Haematol* 68:17, 1988
133. Yoshida Y, Oguma H, Maekawa T: Refractory myelodysplastic anaemias with hypocellular bone marrow. *J Clin Pathol* 41:763, 1995