Review article

The World Health Organization (WHO) classification of the myeloid neoplasms

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A World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms has recently been published. This classification was developed through the collaborative efforts of the Society for Hematopathology, the European Association of Hematopathologists, and more than 100 clinical hematologists and scientists who are internationally recognized for their expertise in hematopoietic neoplasms. For the lymphoid neoplasms, this classification provides a refinement of the entities described in the Revised European-American Lymphoma (REAL) Classification—a system that is now used worldwide. To date, however, there has been no published explanation or rationale given for the WHO classification of the myeloid neoplasms. The purpose of this communication is to outline briefly the WHO classification of malignant myeloid diseases, to draw attention to major differences between it and antecedent classification schemes, and to provide the rationale for those differences. (Blood. 2002;100:2292-2302)

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Introduction

Recently, the World Health Organization (WHO), in conjunction with the Society for Hematopathology and the European Association of Hematopathology, published a new classification for hematopoietic and lymphoid neoplasms.[1] The concepts that underlie this classification were derived from numerous published clinical and scientific studies and from the experience of more than 100 pathologists, clinicians, and scientists from around the world who collaborated to develop this consensus classification.[2] A basic principle of the WHO system is that the classification of hematopoietic and lymphoid neoplasms should utilize not only morphologic findings but also all available information, including genetic, immunophenotypic, biologic, and clinical features to define specific disease entities. Essentially, the WHO classification attempts to incorporate those disease characteristics that have proved to have clinical and biologic relevance into a useful, working nomenclature.

For the lymphoid neoplasms, the WHO classification provides refinement of the entities defined in the Revised European-American Lymphoma (REAL) Classification—a system that is now widely used by pathologists and clinicians.[3] The WHO classification of myeloid neoplasms includes many of the criteria of the French-American-British (FAB) Cooperative Group classifications of acute myeloid leukemia (AML)[4] and myelodysplastic syndromes (MDS)[5] as well as guidelines of the Polycythemia Vera Study Group (PVSG) for the chronic myeloproliferative diseases (CMPDs),[6,7] but there are some significant differences. The purpose of this communication is to outline briefly the WHO classification of the myeloid neoplasms, to draw attention to major differences between the WHO and previous classifications of these disorders, and to provide the rationale for these differences. In addition, we wish to address and clarify specific issues concerning the classification that have appeared both prior and subsequent to the publication of the WHO monograph. The WHO classification of the myeloid neoplasms is outlined in Tables 1 to 7. The detailed criteria for each subtype can be found in the WHO monograph.[1]

Prerequisites for the diagnosis of myeloid neoplasms by the WHO classification

The WHO classification is similar to the FAB and PVSG schemes in that it relies on morphologic, cytochemical, and immunophenotypic features of the neoplastic cells to establish their lineage and degree of maturation. As was true for antecedent classifications, the WHO recognizes the practical importance of the "blast count" in categorizing myeloid diseases and in predicting prognosis. Therefore, the WHO attempts to clearly define "blasts" and to clarify specific issues regarding their accurate and reproducible enumeration. Some of the criteria for blast morphology differ from those in previous classifications.

The blast percentage and assessment of degree of maturation and dysplastic abnormalities in the neoplastic cells should be determined, if possible, from a 200-cell leukocyte differential performed on a peripheral blood smear and a 500-cell differential performed on marrow aspirate smears stained with Wright Giemsa or May-Grünwald Giemsa. The blast percentage should be correlated with an estimate of the blast count from the marrow biopsy section. In addition to myeloblasts, the monoblasts and promonocytes in acute monoblastic/monocytic and acute and chronic myelomonocytic leukemia and the megakaryoblasts in acute megakaryoblastic leukemia are considered as "blast equivalents" when the requisite percentage of blasts is calculated for the diagnosis of AML. In acute promyelocytic leukemia (APL), the blast equivalent is the abnormal promyelocyte. This latter cell is usually characterized by a reniform or bilobed nucleus, but its cytoplasm may vary from heavily granulated with bundles of Auer rods to virtually agranular. A recent, detailed morphologic analysis of the abnormal promyelocytes in APL has led to a better appreciation of the cytologic variability of the leukemic cells in this disorder.[8] Erythroid precursors (erythroblasts) are not included in the blast count except in the rare instance of "pure" erythroleukemia. Dysplastic micromegakaryocytes are also excluded from the

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blast percentage. Although assessment of the number of cells that express the antigen CD34 provides valuable data for diagnostic and prognostic purposes, the percentage of CD34$^+$ cells should not be considered a substitute for a blast count from the smears or an estimate from the bone marrow biopsy. Although CD34$^+$ hematopoietic cells generally are blasts, not all blasts express CD34.[9]

The percentage of blasts proposed by the WHO to categorize a specific case is the percent blasts as a component of all nucleated marrow cells, with the exception of acute erythroleukemia (see below). If a myeloid neoplasm is found concomitantly with another hematologic neoplasm—for example, therapy-related AML and plasma cell myeloma—the cells of the nonmyeloid neoplasm should be excluded when blasts are enumerated. Cytochemical studies (myeloperoxidase, nonspecific esterase) and/or immunophenotyping studies (detection of myeloid-related antigens, such as CD117, CD13, CD33) must provide evidence that the neoplastic cells belong to one or more of the myeloid lineages[10,11] unless this is obvious from specific morphologic findings, such as Auer rods. (Note: The term "myeloid" refers, in this paper, to bone marrow–derived cells, including granulocytes, monocytes, erythroid, and megakaryocytic lineages.)

The WHO classification for AML, MDS, and MPD includes specific genetic subcategories; thus, determination of genetic features of the neoplastic cells must be performed if possible. Many recurring genetic abnormalities in the myeloid neoplasms can be identified by reverse transcriptase–polymerase chain reaction (RT-PCR) or fluorescent in situ hybridization (FISH), but cytogenetic studies should be performed initially and at regular intervals throughout the course of the disease for establishing a complete genetic profile and for detecting genetic evolution. Although it has been suggested that the lack of immediate availability of genetic information is an obstacle to the utilization of the WHO classification,[12] currently available technology should allow assimilation of genetic data in a time frame that will allow appropriate categorization and therapy. It is anticipated that future advances in technology will result in more rapid availability of genetic information.

Acute myeloid leukemia

During the nearly 3 decades that the FAB system was used for classifying AML, it was discovered that many cases of AML are associated with recurring genetic abnormalities that affect cellular pathways of myeloid maturation and proliferation. The FAB classification, initially proposed in 1976,[4] provided a consistent morphologic and cytochemical framework in which the significance of the genetic lesions could be appreciated. In some instances, such as APL and acute myelomonocytic leukemia with abnormal eosinophils (M4Eo), the morphologic characteristics predict the genetic abnormalities. However, morphologic-genetic correlations are not always perfect, and the genetic findings may predict the prognosis and biologic properties of the leukemia more consistently than does morphology. Furthermore, in many cases either there is no correlation between morphology and genetic defects or the underlying genetic and molecular defects cannot be identified. Thus, although the FAB classification recognizes the morphologic heterogeneity of AML, it does not always reflect the genetic or clinical diversity of the disease.

Some investigators suggest that a more relevant classification of AML can be achieved if 2 distinctive subgroups with different biologic features are recognized: (1) AML that evolves from MDS or has features similar to those found in MDS and (2) AML that arises de novo without significant myelodysplastic features.[13,14] The characteristics associated with these 2 groups indicate that they have fundamentally different mechanisms of leukemogenesis. MDS-related leukemia is associated with multilineage dysplasia, poor-risk cytogenetic findings that often include loss of genetic material, and a poor response to therapy. The incidence of this type increases with age, consistent with the hypothesis that MDS and MDS-related leukemia arise through multiple insults to the genetic constitution of the hematopoietic stem cell that occur over time. In contrast, de novo AML usually lacks significant multilineage dysplasia, is often associated with good-risk cytogenetic abnormalities, particularly certain recurring chromosomal translocations and inversions, and often has a favorable response to appropriate therapy, with good failure-free and overall survival times.[15,16] This type of leukemia has a relatively constant incidence throughout life and is the type most likely to be observed in children and young adults.[13] It is probable that specific genetic events associated with these leukemias, which often involve transcription factors, are a major, rate-limiting step in their pathogenesis.[17]

The concept that these and other subgroups of AML can be recognized and classified as unique diseases through correlation of morphologic, genetic, and clinical data is a major theme of the WHO classification and serves as the basis for the 2 most significant differences between it and the FAB classification: (1) a lower blast threshold for the diagnosis of AML in the WHO classification and (2) the categorization of cases of AML into unique clinical and biologic subgroups in the WHO classification.

In the WHO classification, the blast threshold for the diagnosis of AML is reduced from 30% to 20% blasts in the blood or marrow. In addition, patients with the clonal, recurring cytogenetic abnormalities t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22), and t(15;17)(q22;q12) should be considered to have AML regardless of the blast percentage (Table 1).

A number of studies indicate that patients with 20% to 29% blasts in their blood or bone marrow often have similar clinical features—including response to therapy and survival times—as

Table 1. WHO classification of acute myeloid leukemia

Acute myeloid leukemia with recurrent genetic abnormalities
    Acute myeloid leukemia with t(8;21)(q22;q22), (*AML1/ETO*)
    Acute myeloid leukemia with abnormal bone marrow eosinophils and
    inv(16)(p13q22) or t(16;16)(p13;q22), (*CBFβ/MYH11*)
    Acute promyelocytic leukemia with t(15;17)(q22;q12), (*PML/RARα*) and variants
    Acute myeloid leukemia with 11q23 (*MLL*) abnormalities

Acute myeloid leukemia with multilineage dysplasia
    Following MDS or MDS/MPD
    Without antecedent MDS or MDS/MPD, but with dysplasia in at least 50% of
    cells in 2 or more myeloid lineages

Acute myeloid leukemia and myelodysplastic syndromes, therapy related
    Alkylating agent/radiation–related type
    Topoisomerase II inhibitor–related type (some may be lymphoid)
    Others

Acute myeloid leukemia, not otherwise categorized
    Classify as:
        Acute myeloid leukemia, minimally differentiated
        Acute myeloid leukemia without maturation
        Acute myeloid leukemia with maturation
        Acute myelomonocytic leukemia
        Acute monoblastic/acute monocytic leukemia
        Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
        Acute megakaryoblastic leukemia
        Acute basophilic leukemia
        Acute panmyelosis with myelofibrosis
        Myeloid sarcoma

those with 30% or more blasts. According to the FAB criteria for MDS, patients with 20% to 29% blasts in the blood or marrow are classified in the MDS subgroup of refractory anemia with excess of blasts in transformation (RAEBT).[5] In the WHO proposal, most patients with 20% to 29% blasts and myelodysplasia will be classified as AML with multilineage dysplasia—a subgroup that includes patients with a prior history of MDS as well as patients who present initially with AML and dysplasia in multiple cell lines. AML with multilineage dysplasia can be considered the most advanced manifestation of MDS.

Numerous reports indicate that a significant number of patients with RAEBT and AML with myelodysplastic-related features share several important biologic and clinical features. According to some studies, myeloid cells from patients with RAEBT and MDS-related AML have nearly identical profiles of proliferation and apoptosis that differ from those in refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), and refractory anemia with excess blasts (RAEB).[18] Poor-risk cytogenetic abnormalities, including abnormalities of chromosome 7 and complex abnormalities, increased expression of multidrug-resistance glycoproteins, and poor response to chemotherapy, are also common in RAEBT and in MDS-related AML.[14,19] Some investigators have also reported that, when matched for similar disease features, such as white blood cell count or cytogenetic abnormalities, patients with RAEBT and AML have similar survival times if treated with identical therapy.[20-22] In addition, data from the International MDS Risk Analysis Workshop indicate that RAEBT is not an indolent disease. In that study, 25% of patients with 20% to 30% blasts evolved to AML in 2 to 3 months, 50% in 3 months, and more than 60% developed AML within 1 year. The median survival time for patients with RAEBT was less than 1 year.[23]

We suggest that the sum of these data indicates that patients with 20% to 29% blasts in the blood and/or bone marrow accompanied by multilineage myelodysplasia have essentially the same disease as do those with AML with multilineage dysplasia and 30% or more blasts and should be classified in the same category. It is important to emphasize that therapeutic decisions for patients with MDS-related AML should be based not only on the percentage of blasts but also on clinical findings, the rate of disease progression, and genetic data. The effect on the blast percentage of any previous therapy, such as growth factor therapy, must also be taken into account. These cautionary notes apply regardless of whether the blast count is 20%, 30%, or more in a patient with myelodysplastic-related disease.

The lower blast percentage required for a diagnosis of AML also addresses another issue: the classification of patients who have no evidence of multilineage myelodysplasia—that is, patients with true de novo AML—as RAEBT because their blood or bone marrow specimens have fewer than 30% blasts on the initial evaluation. If the leukemia manifests no evidence that it is myelodysplastic related, it does not seem justified to categorize it as a myelodysplastic syndrome. Such a designation could result in inappropriate stratification for risk-determined therapy. Patients with the specific recurring cytogenetic abnormalities t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22), and t(15;17)(q22;q12) should be classified as having AML regardless of the blast percentage.

Three unique subgroups of acute myeloid leukemia are recognized by the WHO classification (Table 1): (1) AML with recurrent genetic abnormalities, (2) AML with multilineage dysplasia, and (3) AML and MDS, therapy related. Cases that do not satisfy the criteria for any of these subgroups, or for which no genetic data

can be obtained, should be classified as one of the entities in a fourth subgroup: AML, not otherwise categorized.

Acute myeloid leukemia with recurrent genetic abnormalities

In the subgroup "AML with recurrent genetic abnormalities," the WHO recognizes 4 well-defined recurring genetic abnormalities (Table 1) that are usually associated with de novo AML. They are commonly encountered: nearly 30% of patients with AML will have one of these genetic abnormalities.[24-26] In cases of AML with t(15;17), t(8;21), and inv(16) or t(16;16), there is such a strong correlation between the genetic findings and the morphology that the genetic abnormality can usually be predicted from the microscopic evaluation of the blood and marrow specimens. Furthermore, because AMLs associated with these abnormalities have distinctive clinical findings and a favorable response to appropriate therapy, they can be considered as truly distinct clinicopathologic-genetic entities.[15,16,25,26] Although abnormalities of 11q23 are often associated with myelomonocytic or monocytic differentiation, AML associated with this abnormality cannot always be predicted with any degree of confidence from the morphology alone.

As noted above, the leukemias associated with these recurrent genetic abnormalities generally have the features of de novo AML. However, all of the genes affected in this group are apparently vulnerable to damage caused by certain types of chemotherapy, specifically with topoisomerase II inhibitors, and can be involved in some cases of therapy-related leukemia.[27,28] In these instances, the unique clinical background indicates that the case should be classified as therapy-related AML.

It is anticipated that the list of entities included in this subgroup will expand in the future. Some members of the WHO committees suggested that other recurring genetic abnormalities, such as t(8;16), t(6;9), or t(3;3), should be included in the current listing. Although these latter genetic abnormalities are often associated with unique morphologic and/or clinical features, it is not yet clear whether they define a unique disease or are mainly of prognostic significance within other subgroups. Furthermore, at least some of the recurring genetic abnormalities—for example, t(3;3)—are more frequently associated with myelodysplastic-related disease than with de novo AML and would be better incorporated into the subgroup of AML with multilineage dysplasia.

It has been suggested that the WHO classification cannot realistically be used for AML because genetic information is not always available in a timely manner.[12] Alternatively, a "realistic" classification has been proposed that permits cases to be classified if the morphologic findings are "suggestive" of a specific genetic abnormality even without adequate knowledge that such a genetic defect is actually present.[12] We agree that the lack of complete information is a problem, but because the genetic data often predict response to treatment and prognosis and often drive treatment decisions, hematologists and pathologists are appropriately under pressure to obtain this information in a timely manner. Furthermore, although the recurring genetic abnormalities are often associated with distinctive morphologic findings, identification of the genetic defect provides a more objective, reproducible means of identifying a specific lesion. For example, the detection of the *CBFβ/MYH11* (inv(16) or t(16;16)) by molecular and/or cytogenetic techniques is reported to correlate with the morphologic diagnosis of M4Eo in 30% to 100% of cases.[29-31] Although the reason for this reported variability is unclear, what is clear is that if the inv(16) is present, the "real" classification is AML with inv(16). In daily practice one often cannot put a given specimen into a

precise disease category without more information than is available at the time—a problem that is by no means confined to the diagnosis of a particular category of AML. We believe that in a case of AML with morphologic features suggestive of a specific genetic abnormality, but for which complete information is not yet available, the pathologist should issue a report that indicates the case may belong to a particular genetic category but that more data are required to prove it. The report should indicate what data are needed and whether the studies are in progress or if a new specimen is necessary. However, we strongly believe that a classification that includes categories that are suggestive of a specific genetic entity for cases that are "not-quite-yet-classifiable" is not what is necessary to solve the problem of the lack of timely information. What is needed instead is a carefully worded report that informs the clinician of what more needs to be done to accurately complete the diagnosis.

Acute myeloid leukemia with multilineage dysplasia

The WHO classification "AML with multilineage dysplasia" recognizes the biologic and clinical importance of MDS-related AML. The diagnosis of this subtype is readily established in patients in whom there is a well-documented history of MDS or a myelodysplastic/myeloproliferative disease (MDS/MPD) that has been present for at least 6 months prior to the onset of overt AML (Table 1). However, the definition of MDS-related AML is more difficult for those cases that present initially as acute leukemia. Whether morphologic, genetic, biologic, clinical features, or some combination of these should be used as defining characteristics was a point of controversy among members of the WHO committees. For practical purposes and worldwide usage, however, it was agreed that morphologic evidence of multilineage dysplasia would be the most universally available marker for its recognition. In the WHO classification, the diagnosis of AML with multilineage dysplasia without antecedent MDS or MDS/MPD is made when blasts constitute at least 20% of the blood or marrow cells and when 50% or more of the cells in 2 or more myeloid lineages are dysplastic in a pretreatment sample. Although the 50% figure may appear high, it is derived from a number of studies that indicate that a lower threshold of dysplasia may not consistently identify AML with MDS-like features.[32-35] In some studies, multilineage dysplasia is an independent prognostic factor only in patients who have favorable cytogenetics but has no additional adverse impact in patients with poor-risk genetics.[35] We suggest that a combination of genetic and morphologic studies may ultimately be used to further characterize this type of leukemia.

Acute myeloid leukemias and myelodysplastic syndromes, therapy related (t-AML and t-MDS)

Two types of t-AML and t-MDS are recognized in the WHO classification, depending on the causative therapy: an alkylating agent/radiation–related type and a topoisomerase II inhibitor–related type.

Alkylating agent/radiation–related t-AML and t-MDS. This disorder usually appears 4 to 7 years after exposure to the mutagenic agent. Approximately two thirds of cases present with MDS and the remainder as AML with myelodysplastic features.[36-40] It could be disputed whether a distinct category is needed for alkylating agent–related AML, because it is similar to AML with multilineage dysplasia and could be placed in that category.[12] However, the identification of a known, predisposing etiologic agent is but one major difference between these 2 groups; there is also a higher incidence of abnormalities involving chromosomes 5 and/or 7 and a worse clinical outcome in the therapy-related group.[36-39]

Topoisomerase II inhibitor–related AML. In contrast to alkylating agent–related t-AML and t-MDS, acute leukemia secondary to topoisomerase II inhibitors often does not have a preceding myelodysplastic phase, and it most frequently presents as overt acute leukemia, often with a prominent monocytic component.[27,28,41-44] The latency period between the initiation of treatment with topoisomerase II inhibitors and the onset of leukemia is short, ranging from 6 months to 5 years, with median times of 2 to 3 years usually reported.[27,28,41-43] Most often, this type of t-AML is associated with balanced translocations involving chromosome bands 11q23 or 21q22.[27,28,42-44] However, other translocations including inv(16)(p13q22) or t(15;17)(q22;q12) have been reported, and in these latter instances, as with 11q23 and 21q22 abnormalities, the morphologic and clinical findings are similar to those observed in patients with these translocations and no history of prior cytotoxic therapy.[27,28] The initial response to therapy of topoisomerase II inhibitor–related AML as well as the overall survival are reported to be similar to cases of de novo AML with the corresponding genetic abnormality.[28] Acute lymphoblastic leukemia associated with 11q23 abnormalities—for example, t(4;11)(q21;q23)—may also result from topoisomerase II therapy.[28,45,46]

In summary, we believe it is important to identify cases of therapy-related acute leukemia and MDS. These disorders have proved to be models for a better understanding of the pathogenesis of leukemias that arise without preceding therapy, and knowledge gained from their study may lead to more specific and directed therapies for de novo as well as therapy-related cases.

Acute myeloid leukemia, not otherwise categorized

The group "acute myeloid leukemias, not otherwise categorized" (NOC) is intended to provide a framework for classification of cases that do not satisfy criteria for one of the other major categories. One of the primary considerations for the WHO classification of AML is the universality of application. The resources of hematology laboratories worldwide vary substantially. Although the ideal evaluation of patients with acute leukemia includes cytogenetic and, if necessary, molecular genetic studies, we recognize that these resources are not universally available at the present time. Careful morphologic evaluation can provide very significant information, such as multilineage dysplasia, and will result in appropriate classification in many cases. Furthermore, although direct clinical-genetic correlations are not presently recognized for many of the cases classified as AML, NOC, we anticipate that future studies may uncover relevant clinical, genetic, and morphologic profiles.

In most respects, the entities included in this group are defined almost identically as the corresponding entity in the previous FAB classification,[4] and the criteria for their recognition are based principally on identification of the major cell lineage(s) involved and the degree of maturation. However, 2 subtypes in this category, acute erythroid leukemia and acute panmyelosis with myelofibrosis, deserve special comment.

Acute erythroid leukemia. Acute erythroid leukemia is characterized by a predominant erythroid proliferation in the bone marrow. Recently, attention has been focused on the heterogeneity of neoplasms of erythroid cells and, in particular, on those that are composed mainly of primitive erythroid precursors with a minimal, if any, myeloblastic component.[47-51] These latter cases may not meet the requirements of the FAB classification for a diagnosis of acute leukemia.

The WHO classification recognizes 2 subtypes of acute erythroid leukemia, based on the presence or absence of a significant myeloblastic component. The first type, acute erythroid/myeloid leukemia, is defined as having at least 50% erythroid precursors in the entire marrow nucleated cell population and myeloblasts that account for at least 20% of the nonerythroid cell population. It corresponds to AML M6 in the FAB classification. All stages of erythroid maturation are found with a variable shift toward erythroid immaturity. Some cases that meet the criteria for acute erythroid/myeloid leukemia will also meet the criteria for AML with multilineage dysplasia. If that is the case, we would suggest that a diagnosis of "AML with multilineage dysplasia, acute erythroid/myeloid type" be made.

The second subtype of acute erythroid leukemia recognized by the WHO is "pure erythroid leukemia," characterized by the proliferation of immature cells committed exclusively to the erythroid lineage. In this disease, 80% or more of all marrow cells are immature erythroid precursors with minimal differentiation, and there is no significant myeloblastic component. Although the blast cell morphology usually suggests their erythroid origin, in some cases they may be so primitive that proving their lineage is difficult.[47,49,51] This erythroid neoplasm has been referred to previously as DiGuglielmo disease, acute erythremic myelosis, true erythroleukemia, and minimally differentiated erythroleukemia.[47-52]

Acute panmyelosis with myelofibrosis. Acute panmyelosis with myelofibrosis (APMF) is an acute myeloid disorder with an unfavorable prognosis.[53] Although it is uncommon (fewer than 1%-2% of all cases of acute leukemia), when APMF is encountered the fibrosis may cause considerable difficulty in arriving at a correct diagnosis.[54] The critical point is to recognize that it is an acute process that has sufficient numbers of blasts to be considered AML. It is often associated with dysplasia and immaturity in multiple cell lines, with a prominent megakaryoblastic and megakaryocytic population. We believe that the diseases known as acute myelosclerosis, acute myelofibrosis, acute myelodysplasia with myelofibrosis, and malignant myelosclerosis[53,55-57] are synonymous with APMF. It is necessary to distinguish this entity from chronic idiopathic myelofibrosis (CIMF) as well as from lower grades of MDS associated with myelofibrosis. Some morphologic features of APMF overlap AML with multilineage dysplasia with the addition of myelofibrosis; whether these are 2 manifestations of the same process is unclear. At present, we suggest that they be recognized as individual entities. There is also some controversy about the relationship of APMF to acute megakaryoblastic leukemia.[58,59] The WHO committee recognized this problem. If the leukemia is predominantly megakaryoblastic with myelofibrosis, we suggest the term "acute megakaryoblastic leukemia with myelofibrosis." If the process is a panmyelopathy with myelofibrosis, we suggest the term "acute panmyelosis with myelofibrosis."

Myelodysplastic syndromes (MDS)

Since its introduction in 1983, numerous studies have documented the clinical utility of the FAB classification of MDS for predicting prognosis and evolution to acute leukemia.[23,60-63] In essence, these studies have validated the contributions of a morphologic classification scheme for MDS that incorporates a careful assessment of the number of blasts in the blood and bone marrow and of the cell lineages that are affected by the neoplastic process.[23]

The WHO classification incorporates many of the concepts and definitions of the FAB system, but it also recognizes recently published data to refine the definition of some subtypes and thus to improve their clinical relevance. The most important difference between the WHO and FAB classifications is the lowering of the blast threshold for the diagnosis of AML from 30% to 20% blasts in the blood or bone marrow. As a result, the FAB category RAEBT is eliminated from the WHO proposal (Table 2). Other changes include a refinement of the definitions for the lower-grade lesions, RA and RARS, and the addition of a new category, refractory cytopenia with multilineage dysplasia (RCMD). Two subtypes of RAEB, RAEB-1 with 5% to 9% marrow blasts and RAEB-2 with 10% to 19% marrow blasts, are also recognized. They take into account data published by the International MDS Risk Analysis Workshop that patients with 10% or more blasts in the bone marrow have a worse clinical outcome than do those with fewer blasts.[23] The WHO classification also recognizes the "5q− syndrome" as a unique, narrowly defined entity. Lastly, because of the controversy as to whether chronic myelomonocytic leukemia (CMML) is a myelodysplastic or a myeloproliferative disease, this disorder has been placed in a newly created disease group, MDS/MPD.

In the WHO system, patients with blood or bone marrow specimens that show at least 20% blasts are considered AML, thus eliminating the FAB category RAEBT. The rationale for this change has been described under the "Acute myeloid leukemia" section.

The WHO classification refines the definition of RA and RARS and introduces a new category, RCMD (Table 2). The FAB guidelines for RA and RARS are somewhat ambiguous and result in different interpretations by different observers. They state that, in RA and RARS, "morphological abnormalities in the granulocytic and megakaryocytic series identical to those present in the other subtypes of MDS may occasionally be found in varying degrees." But they also note that the "erythroid series is mainly affected . . . and the granulocytic and megakaryocytic series almost always appear normal."[5] However narrowly or loosely one interprets these criteria, in practice and in published series RA and RARS include a heterogeneous population of patients, ranging from those with unilineage dysplasia restricted to the erythroid cells to those also manifesting severe dysplasia in the granulocytic and megakaryocytic lineages.

A number of studies have shown that, in cases diagnosed as RA or RARS by FAB criteria, the finding of multilineage dysplasia imparts a worse prognosis than if only erythroid dysplasia is present. In RARS, patients with dysplasia restricted to the erythroid series have signs, symptoms, and complications related mainly to anemia, whereas patients with RARS and multilineage dysplasia may also experience complications related to granulocyte or platelet abnormalities.[64,65] Those with only dyserythropoiesis are reported to have longer survival times and a lower rate of transformation to AML and, in contrast to those with multilineage dysplasia, the risk of transformation may not increase significantly throughout the course of the disease.[64] These findings suggest that RARS with unilineage dysplasia is, in most cases, a different disease than RARS with multilineage dysplasia. Similar data are available to indicate that RA, as defined by FAB guidelines, is likewise heterogeneous. In contrast to patients with RA and only dyserythropoiesis, patients with multilineage dysplasia have bicytopenia or pancytopenia, a higher incidence of cytogenetic abnormalities, more frequent progression to AML, and shorter survival.[66-69]

In the WHO classification, RA and RARS are defined as diseases in which dysplasia is morphologically restricted to the erythroid lineage (Table 2). If there is multilineage dysplasia—that is, 10% or more dysplastic cells in 2 or more of the myeloid lineages—and fewer than 5% blasts, no Auer rods, and no monocytosis, the diagnosis is RCMD. In cases of RCMD with at least 15% ringed sideroblasts, the diagnosis is

Table 2. WHO classification and criteria for the myelodysplastic syndromes

Disease	Blood findings	Bone marrow findings
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia *only* < 5% blasts < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia *only* ≥ 15% ringed sideroblasts < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods < 1 × 10⁹/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines < 5% blasts in marrow No Auer rods < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods < 1 × 10⁹/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines ≥ 15% ringed sideroblasts < 5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias < 5% blasts No Auer rods < 1 × 10⁹/L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods ± < 1 × 10⁹/L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes < 5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia < 5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts No Auer rods Isolated del(5q)

RCMD with ringed sideroblasts (RCMD-RS). Whether there are major clinical or biologic differences between RCMD and RCMD-RS is not yet clear. Data recently published by Germing and associates in a study that included 284 patients with RCMD showed no significant difference in survival or progression to AML between RCMD and RCMD-RS.[69]

A study by Nosslinger et al has taken exception to the WHO proposal in regard to the benefit of further subtyping RA and RARS patients according to the finding of multilineage dysplasia. In their study, patients with RCMD had a better survival than did those with RA or RARS.[70] However, in that study, not only were the WHO criteria for RCMD not used but a number of patients classified as having RA and RARS had neutropenia and/or thrombocytopenia, which would not be expected if these diseases were also defined by the WHO criteria.

An important problem in this group of diseases is the possibility of misdiagnosis of MDS due to overinterpretation of dyspoiesis that is secondary to a nonclonal disorder. This is particularly problematic in the diagnosis of RA. Erythroid dysplasia is difficult to define precisely, and the threshold for its recognition is variable from one observer to another. The WHO classification does not entirely eliminate this problem, but the establishment of minimal quantitative thresholds of dysplasia for RA, RARS, RCMD, and RCMD-RS should result in more consistency and accuracy in diagnosis. Whether RARS with unilineage erythroid dysplasia, as defined in the WHO classification, is a myelodysplastic disorder remains to be determined. However, until more reliable markers of erythroid dysplasia are widely available, the category of RA will likely continue to include some cases that are nonclonal erythroid disorders. In addition, occasional patients may present with cytopenias affecting more than one cell lineage and have multilineage dysplasia but not at the 10% level required for a diagnosis of RCMD. If blasts are fewer than 5% in the bone marrow, such cases are difficult to classify or even to recognize as MDS with confidence. In cases like these a presumptive diagnosis of RCMD might be appropriate. However, in such cases as well as for cases suspected to be RA, if there is no evidence of clonality by genetic studies, the WHO recommends observation for 6 months prior to making a diagnosis of MDS.

RAEB is divided into 2 subgroups, RAEB-1 and RAEB-2, depending on the number of blasts in the blood and bone marrow (Table 2).

Data from the International Workshop on Prognostic Factors in MDS indicated that patients with 10% or more blasts in the bone marrow have a shorter median survival and a higher rate of transformation to acute leukemia than do those with fewer than 10% blasts.[23] In view of these data, the WHO classification recognizes 2 groups of patients with RAEB, RAEB-1 and RAEB-2, depending on the percentage of blasts in the blood and marrow and the presence or absence of Auer rods. The criteria for each subgroup are outlined in Table 2.

One myelodysplastic syndrome is defined by a specific cytogenetic abnormality, the 5q− syndrome.

Table 3. WHO classification of the myelodysplastic/myeloproliferative diseases

Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia
Juvenile myelomonocytic leukemia
Myelodysplastic/myeloproliferative disease, unclassifiable

Although deletions of 5q may be observed in a wide spectrum of de novo and therapy-related acute myeloid leukemias and myelodysplastic processes, the 5q− syndrome is narrowly defined as de novo MDS with an isolated cytogenetic abnormality involving deletions between bands q21 and q32 of chromosome 5. Detailed mapping experiments of this region of chromosome 5 have provided evidence that the gene(s) involved in this syndrome is different than that affected in other subgroups of MDS and AML associated with del(5q).[71,72] In the 5q− syndrome there is usually a refractory macrocytic anemia, normal to increased platelet count, and increased numbers of megakaryocytes, many of which have hypolobated nuclei. The number of blasts in the bone marrow and blood is less than 5%.[73,74] There is usually long survival. Additional cytogenetic abnormalities or 5% or more blasts in the blood or marrow is exclusionary for the diagnosis. Similar to AML, it is anticipated that additional myelodysplastic syndromes with a characteristic constellation of clinical, genetic, and pathologic findings will be identified.

Chronic myelomonocytic leukemia is eliminated from the MDS category and placed in a group of myeloid disorders with features of both myelodysplasia and myeloproliferative diseases, MDS/MPD (Table 3; discussion below).

Myelodysplastic/myeloproliferative diseases (MDS/MPD)

The MDS/MPD category includes myeloid disorders that have both dysplastic and proliferative features at the time of initial presentation and that are difficult to assign to either the myelodysplastic or myeloproliferative group of diseases. The 3 major disorders that constitute this group are chronic myelomonocyic leukemia (CMML), atypical chronic myeloid leukemia (aCML), and juvenile myelomonocytic leukemia (Table 3). The WHO classification provides a less restrictive view of these diseases than do previous classification schemes that arbitrarily assigned them to either the MDS or MPD category.[5,75] For individual patients, the clinician may view the patient in the context of whether proliferative or dysplastic manifestations predominate and treat accordingly. For cooperative groups and clinical investigators, the WHO category of MDS/MPD may allow for more focused clinical and scientific investigation of these entities that overlap 2 major disease categories. The criteria for the recognition of these disorders are detailed in the WHO monograph, but some aspects of CMML and aCML are particularly problematic and warrant some comment here.

Chronic myelomonocytic leukemia (CMML)

CMML has generated considerable controversy among a number of investigators as to whether it is primarily a myeloproliferative (MPD) or myelodysplastic (MDS) disease or both.[76,77] The FAB group recommended that patients who meet the criteria for the diagnosis of CMML be subdivided into CMML, MDS-like or CMML, MPD-like, depending on the degree of leukocytosis.[75] Clinical studies that divided patients according to the FAB suggestions, however, concluded that the magnitude of the white blood cell count does not identify subgroups that have major biologic or prognostic differences.[78,79] To date, no specific cytogenetic or molecular differences between patients with predominantly MDS or MPD characteristics have been reported. Furthermore, some patients who initially manifest as having "nonproliferative" CMML, with low white blood cell counts and minimal if any splenomegaly, may eventually become quite "proliferative," with markedly elevated white blood cell counts.[78] For these reasons, the WHO committees chose not to divide CMML into these 2 subtypes. To emphasize the nosologic issues, CMML is placed in a separate category of diseases, the name of which clearly states the problem.

The WHO classification does not make any significant changes in the criteria for the diagnosis of CMML (Table 4). Despite the controversy over the disease category to which CMML belongs, there is one issue about which all investigators agree: the higher the blast count in CMML, the more unfavorable the prognosis.[77,79-82] As a result, the WHO divides CMML into 2 prognostic categories, CMML-1 and CMML-2, based on the number of blasts in the blood and bone marrow (Table 4).

Atypical chronic myeloid leukemia (aCML)

"Atypical chronic myeloid leukemia" is not an ideal name for any disease, because it implies that the associated disorder is merely an atypical variant of chronic myelogenous leukemia (CML). Instead, aCML lacks the Philadelphia (Ph) chromosome and *BCR/ABL* fusion gene that are the hallmarks of classic CML. In addition, aCML is associated with marked granulocytic and often multilineage dysplasia, which is not observed during the chronic phase of CML. The few clinical studies published to date indicate that aCML is clinically a very aggressive disease, with reported median survival times of only 11 to 18 months.[83,84] Although the WHO committees struggled for a better name for aCML to avoid the possibility of confusion with CML, none could be agreed upon. However, the placement of aCML in a different disease category does serve to set it apart from CML.

Juvenile myelomonocytic leukemia (JMML)

JMML is a clonal hematopoietic disorder characterized by proliferation principally of the neutrophil and monocytic lineages. It lacks the Ph chromosome and *BCR/ABL* fusion gene and manifests as a leukemic disorder in infants and young children, although adolescents may occasionally be affected as well. The criteria utilized in

Table 4. Diagnostic criteria for chronic myelomonocytic leukemia (CMML)

Persistent peripheral blood monocytosis greater than 1×10^9/L
No Philadelphia chromosome or *BCR/ABL* fusion gene
Fewer than 20% blasts* in the blood or bone marrow
Dysplasia in one or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are present and:
an acquired, clonal cytogenetic abnormality is present in the marrow cells, or
the monocytosis has been persistent for at least 3 months and all other causes of monocytosis have been excluded
Diagnose CMML-1 when blasts fewer than 5% in blood and fewer than 10% in bone marrow
Diagnose CMML-2 when blasts are 5% to 19% in blood, or 10% to 19% in marrow, or if Auer rods are present and blasts are fewer than 20% in blood or marrow
Diagnose CMML-1 or CMML-2 with eosinophilia when the criteria above are present and when the eosinophil count in the peripheral blood is greater than 1.5×10^9/L

*In this classification of CMML, blasts include myeloblasts, monoblasts, and promonocytes.

Table 5. WHO classification of chronic myeloproliferative diseases

Chronic myelogenous leukemia [Ph chromosome, t(9;22)(q34;q11), *BCR/ABL*-positive]

Chronic neutrophilic leukemia

Chronic eosinophilic leukemia (and the hypereosinophilic syndrome)

Polycythemia vera

Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)

Essential thrombocythemia

Chronic myeloproliferative disease, unclassifiable

the WHO classification for JMML follow the guidelines established by the European Working Group of MDS in Childhood.[85] This entity incorporates those leukemias of childhood previously referred to as juvenile chronic myeloid leukemia and chronic myelomonocytic leukemia.[85] Cases previously referred to as the infantile monosomy 7 syndrome are also included in this category.[86]

If future studies provide more definitive evidence that CMML, atypical CML, or JMML are more accurately classified as purely myelodysplastic or myeloproliferative processes, appropriate changes in their classification will be warranted. In our opinion, at the present time such evidence is not available.

Chronic myeloproliferative diseases

The WHO classification of the chronic myeloproliferative diseases (CMPDs) recognizes 7 entities (Table 5). One, CML, is defined not only by its classic morphology and clinical features but also by the genetic abnormality with which it is always associated, the Philadelphia chromosome or *BCR/ABL* fusion gene. Unfortunately, specific genetic abnormalities have not yet been identified for any of the other CMPDs. Therefore, the classification of the CMPDs that lack the *BCR/ABL* fusion gene requires careful correlation of morphologic findings in the blood and bone marrow with clinical and laboratory findings. In particular, the morphologic findings of the bone marrow biopsy figure prominently in the recognition of these diseases. Although the WHO criteria for the CMPDs incorporate recent knowledge and newer disease markers whenever possible, the criteria established by the PVSG remain integral components for the diagnosis of some diseases.

To date, no major issues have been raised regarding the WHO proposals for the CMPDs. Nevertheless, some comments at this point regarding nomenclature and criteria may provide a better understanding of the classification of this category of diseases.

Chronic myelogenous leukemia (CML)

In the WHO proposal, CML is defined specifically as a myeloproliferative disease that is characterized by the invariable presence of the Ph chromosome or the *BCR/ABL* fusion gene. Although in most cases the diagnosis is easily made from morphologic evaluation of the blood smear, confirmation by genetic studies is essential, particularly in view of the advent of therapy that targets the BCR/ABL fusion protein.[87] The WHO committees relied upon the literature as well as upon the collective experience of the clinical advisory committee members to refine the criteria for accelerated and blast phase[88-92] that are outlined in Table 6.

Chronic neutrophilic leukemia (CNL)

The major question regarding CNL is whether it is a real disease. Fewer than 150 cases have been reported in the literature, and in a number of these cases CNL was found in association with another neoplasm, particularly myeloma.[93-95] In a few of the latter cases, molecular studies showed that the neutrophils were not clonal.[96] These latter observations, when coupled with normal cytogenetic studies and the "toxic" neutrophil morphology in most reported cases, raise the possibility that the neutrophilia is due to abnormal cytokine production by an associated tumor or abnormal inflammatory response. However, there are well-characterized cases that do meet the criteria for CNL for which cytogenetic or molecular genetic studies have confirmed clonality of the neutrophil lineage.[97-99] In view of these latter reports, the WHO included CNL in the CMPDs, with the recommendation that the possibility of an underlying disease be carefully excluded. If another neoplasm, such as myeloma, is present, the diagnosis of CNL should be made only if there is genetic evidence of a myeloid neoplasm.

Chronic eosinophilic leukemia (CEL)/hypereosinophilic syndrome (HES)

The decision to list CEL and HES together does not imply that the WHO considers all cases of HES to be clonal myeloproliferative diseases. Rather, it addresses the problem that, in practice, it may be virtually impossible to distinguish between clonal eosinophilia and eosinophilia secondary to abnormal cytokine production for which no etiologic basis is recognized.[100-102] The diagnosis of CEL or HES can be made only after a number of infectious, inflammatory, and neoplastic diseases known to be associated with eosinophilia (including CML, AML with inv(16), other CMPDs, T-cell

Table 6. Criteria for accelerated and blast phases of CML

CML, accelerated phase (AP)

  Diagnose if one or more of the following is present:

    Blasts 10% to 19% of peripheral blood white cells or bone marrow cells

    Peripheral blood basophils at least 20%

    Persistent thrombocytopenia ($< 100 \times 10^9$/L) unrelated to therapy, or persistent thrombocytosis ($> 1000 \times 10^9$/L) unresponsive to therapy

    Increasing spleen size and increasing WBC count unresponsive to therapy

    Cytogenetic evidence of clonal evolution (ie, the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML)

  Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia, should be considered as suggestive of CML-AP. These findings have not yet been analyzed in large clinical studies, however, so it is not clear if they are independent criteria for accelerated phase. They often occur simultaneously with one or more of the other features listed.

CML, blast phase (BP)

  Diagnose if one or more of following is present:

    Blasts 20% or more of peripheral blood white cells or bone marrow cells

    Extramedullary blast proliferation

    Large foci or clusters of blasts in bone marrow biopsy

Table 7. WHO classification of mast cell disease (mastocytosis)

Cutaneous mastocytosis

Indolent systemic mastocytosis

Systemic mastocytosis with associated clonal, hematologic non–mast cell lineage disease

Aggressive systemic mastocytosis

Mast cell leukemia

Mast cell sarcoma

Extracutaneous mastocytoma

lymphoma, Hodgkin lymphoma, and others) have been excluded. Then, if there is no evidence for clonality, the diagnosis of HES is preferred, whereas the finding of a clonal myeloid abnormality would support the diagnosis of CEL.[102]

Chronic idiopathic myelofibrosis (CIMF), prefibrotic stage

The criteria classically utilized for the diagnosis of CIMF include a leukoerythroblastic blood smear, organomegaly due to extramedullary hematopoiesis, and myelofibrosis of the bone marrow.[103] Recently, some investigators have drawn attention to an early, prefibrotic stage of CIMF, in which the classic findings are absent or minimal.[104,105] This early phase of CIMF shares a number of clinical, laboratory, and even morphologic features with the early stages of polycythemia vera (PV) and with essential thrombocythemia (ET). However, the prominent neutrophil proliferation, decreased numbers of erythroid precursors, and marked atypia of the megakaryocytic lineage often aid in distinguishing the prefibrotic stage of CIMF from the other CMPDs. Although these findings must always be correlated with other clinical, laboratory, and genetic studies, the worse survival of CIMF in comparison with ET or PV indicates that recognition of this phase of CIMF is important.

Mast cell disease (mastocytosis)

Mast cells originate from a bone marrow hematopoietic stem cell and demonstrate a number of characteristics that indicate they are myeloid cells. Mastocytosis includes a heterogeneous group of diseases characterized by abnormal growth and accumulation of mast cells in one or more organ systems. Recent data suggest that most variants of systemic mast cell disease are clonal; a somatic mutation of *KIT*, the protooncogene that encodes the tyrosine kinase receptor for stem cell factor, is usually present.[106,107] Although a number of classification schemes have been proposed for mast cell disease, none have been universally accepted. The WHO classification (Table 7) is derived from the Year 2000 Mast Cell Disease Symposium, a conference that brought together nearly 50 clinicians, pathologists, and investigators whose primary interest is mast cell disease. The reader is referred to the published proceedings of that meeting for a detailed analysis of the formulation of this classification of mast cell disease.[108]

Summary

The WHO classification of myeloid neoplasms is intended to link previous, predominantly morphologic classification systems with newly emerging scientific data. It incorporates morphologic, biologic, and genetic information into a working nomenclature that has clinical relevance. Although it could be argued that the classification should have been validated in a large series of patients prior to its publication, the concepts and criteria that form its foundation have in fact already been published and tested in the literature. As new information regarding the molecular pathogenesis of myeloid malignancies accumulates and as therapy is devised to target specific molecular abnormalities, the classification of myeloid diseases must evolve to incorporate the new discoveries. Indeed, plans are already underway by the Society for Hematopathology and the European Association of Hematopathology to continually update the classification. We believe that the WHO classification provides a framework to accommodate such changes.

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