The New WHO Nomenclature: Introduction and Myeloid Neoplasms

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ABBREVIATIONS: ACML = atypical CML; AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; CIMF = chronic idiopathic myelofibrosis; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CMML = chronic myelomonocytic leukemia; CNL = chronic neutrophilic leukemia; DIC = disseminated intravascular coagulation; FAB = French-American-British; JMML = juvenile chronic myelomonocytic leukemia; MDS = myelodysplastic syndromes; MPD = myeloproliferative diseases; REAL = Revised European-American Classification of Lymphoid Neoplasms; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RARS = refractory anemia with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; WHO = World Health Organization.

INDEX TERMS: leukemia; myeloid; nomenclature.

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LEARNING OBJECTIVES

1. Compare and contrast the principles of FAB and WHO classifications for myeloid neoplasms.
2. Categorize presentations into the WHO nomenclature.
3. Justify the percentage of blasts necessary for a diagnosis of acute leukemia in the WHO system.
4. Explain the four parameters on which the WHO classification is based.
5. Describe multi-lineage dysplasia and give examples of peripheral blood and bone marrow characteristics.
6. Summarize the four categories of acute myeloid leukemia in the WHO system.
7. Associate recurrent genetic abnormalities with specific leukemic presentations.
8. Associate therapy related leukemia and myelodysplastic syndromes with chemotherapeutic agents.
9. Describe the entities included in AML, not otherwise categorized.
10. Summarize the five categories of myelodysplastic syndromes included in the WHO classification.
11. Rationalize the creation of the category of MPD/MDS and discuss the disorders included in that category.

Historically, diseases in the form of a single patient were identified and described by a single physician. Because only rarely did two or more physicians see the same type of patient in the same time frame, the classification of most diseases is not as complex as it might otherwise be. Blood cells, on the other hand, were described and named by many different people in many countries many times over. As individuals saw and described cells, they gave them names, and assigned those cells to specific groups with little to no clear understanding of the reality of the cells. To further confuse classification schema were the inherent difficulties in 18th and 19th century lens technology and, until the utilization of the Romanowsky-based stains, the lack of common staining methods.

The result of this early work was the sometimes contradictory cellular nomenclature. This lack of clarity was reflected in the nomenclature of various malignant hematopoietic diseases such as the leukemias. While there was some concern over this lack of clarity, the treatment of the various hematologic malignancies was such that a more definitive schema was not required. However, in 1946, a landmark article reported the first successful treatment of malignancy by chemical means.[1] This work required that naming schema be consistent if one were to utilize the appropriate therapy for these diseases.

The first step was to determine the identity of the various cell forms. Once the nomenclature of individual cells was agreed

Table 1. FAB cytochemical differentiation of acute leukemia presentations

Cell	Wright's stain	Peroxidase	Sudan Black B	Chloro-acetate esterase	α – naphthyl butyrate esterase	naphthol - ASD acetate esterase	PAS (glycogen)
Typical AML picture (M1 to M3)	+/- Auer rods	+ in some blasts	+ in some blasts	+ if some later forms are present	0	0	usually 0
Typical AMMoL picture (M4)		+ in some blasts	+ in some blasts	+ in some blasts	+ in monocytoid forms	++ Na F inhibited	usually 0
Typical AML picture - (M5)		+ in some blasts	+ in some blasts	0	+ in some blasts	++++ Na F inhibition	usually 0
Typical AML picture (M6)	1. megalo-blastoid changes 2. ringed sideroblasts 3. karyolysis	usually 0 may be + if significant myeloid components	usually 0 may be + if significant myeloid components	usually 0 may be + if significant myeloid components	usually 0 may be + if significant myeloid components	0 to ++++	++++ granular
Typical AMegL picture (M7)	1. presence of megakaryoblasts 2. micromega-karyocytes or meg. fragments	0 + for platelet peroxidase	+ in some blasts	+ in some blasts	0	+ in some blasts	usually 0
Typical ALL (L1 - L2 - L3)	0	0	0	0	0	0 or blobs	
Typical stem cell leukemia	0	0	0	0	0	0	

upon, it was the logical next step to reevaluate the nomenclature of the diseases in which these cells or their variants would be found. Through the work of various professional groups such as the Society of Hematology over the last forty years, a more consistent cellular nomenclature has been developed. As a consequence to that effort, the Society of Hematology created a group of practicing hematologists and asked them to develop a system that would reflect both the morphology and cytochemistry of these cells.

The result of their efforts was the French-American-British (FAB) Classification System for Myeloproliferative Diseases, Myelodysplastic Diseases, and Acute Leukemia.[2] This system utilized what was then state of the art cytochemical testing in addition to Romanowsky-based staining reactions for the identification of the variants of acute leukemia (Table 1). A serious flaw in this system for the acute leukemias was the inability to differentiate the acute lymphoblastic leukemias through cytochemical testing. The myeloproliferative and myelodysplastic conditions were differentiated solely on the basis of morphological criteria (Tables 2 and 3). With the advent of immunophenotyping, the FAB Classification was modified to include these tests for the differentiation of the lymphoproliferative disorders but this did not constitute a major reevaluation of the original classification schema. Diagnostic chromosomal testing was limited to the Philadelphia chromosome in chronic myelogenous leukemia.[3] Increases in the sensitivity of cytogenetic techniques and the inclusion of PCR and other molecular diagnostic testing moved the incidence of positivity for the Philadelphia chromosome or its variants to near 95%.[4]

Table 2. FAB classification of the myelodysplastic syndromes

Characteristic	RA*	RARS†	RAEB‡	CMML§	RAEBt+
Leukocyte count	normal to ↓	normal to ↓	normal to ↓	increased	normal to ↓
Monocytes					
bone marrow	-	-	-	at least 20%	-
peripheral blood	-	-	-	>1x10^9/L	-
Concentration of blasts in peripheral blood	<1%	<1%	<5%	<5%	>5%
Concentration of blasts in marrow	<5%	<5%	5% - 20%	5% - 20%	20% - 30%
Dyserythropoiesis	+++	++	+/-	+/-	+/-
Dysgranulopoiesis	-	-	++	++	+/-
Dysmegakaryocytopoiesis	-	-	+/-	+/-	+/-
Siderocytes/ sideroblasts	+	+	+/-	-	+/-
Ringed sideroblasts	+/-	>15%	+/-	-	+/-

* RA = refractory anemia
† RARS = refractory anemia with ringed sideroblasts
‡ RAEB = refractory anemia with excess blasts
§ CMML = chronic myelomonocytic leukemia
+ RAEBt = refractory anemia with excess blasts in transformation

Table 3. FAB Differentiation of myeloproliferative syndromes

	CML*	P V†	E T‡	AMM§	Benign Leukemoid Reaction
WBC (x10^9/L)	>30->100	12 - 25	12 - 20	<30	>12
Platelets (x10^9/L)	mod increase	mod increase	***>1,000***	variable	variable
RBC (x10^{12}/L)	mild anemia	***inc (18-24 g/dL hgb common)***	usually not increased	usually not increased	normal
Fibrosis	late in disease	late in disease	- / +	***prominent***	usually absent
Philadelphia chromosome	***present*** (80%)	absent	absent	absent	absent
Splenomegaly	***present***	***present***	***present***	***prominent***	absent
Leukocyte alkaline phosphatase	***decreased***	increased	normal to increased	increased	***increased***
RBC morphology	normal	normal	normal	***teardrops***	normal
Leukoerythroblastosis	neutrophilia	few NRBCs	minimal	***prominent***	+/- immature granulocytes
Basophilia/eosinophilia	***prominent***	mild	mild	mild - moderate	usually absent
Granulocytic dyspoiesis	***Pseudo-Pelger Huët hypersegmented hypogranular***	rare	rare	rare	rare
Large platelets; micro-megakaryocytes	present	- / +	present	present	usually absent
Hypercellular marrow	present	present	present	present in cellular phase	variable

* CML = chronic myelogenous leukemia
† PV = polycythemia vera
‡ ET = essential thrombocythemia
§ AMM = agnogenic myeloid metaplasia with or without myelofibrosis

Note: Italics indicate defining features

Similarly, the classification of the lymphomas has been rooted in the histologic architecture of the nodes or treatment outcomes, neither of which was satisfactory. In the 1970s, the development of the Working Formation for the non-Hodgkin's lymphomas was begun by clinicians who were unhappy about the lack of clarity that could be provided to them by pathologists. The Working Formulation and the National Cancer Institute's attempts were limited in varying degrees as well.[5] This initiative put great emphasis on clinical outcomes and was not usable by pathologists. In 1994, the Revised European-American Classification of Lymphoid Neoplasms (REAL) was developed through a consensus methodology and published by the International Lymphoma Study group.[6] This work was based in large part on the original and updated Kiel classification which, like the Lukes-Collins system, postulated that

lymphoproliferative diseases should be related to their immune functions as B, T, or NK cells.[7,8]

REAL departed from traditional schemes and presented a new paradigm for the classification of lymphomas. It emphasized the specific grouping of laboratory and clinical features, i.e., cellular morphology, immunophenotyping, genetics, signs, symptoms, and course. It included the site of involvement as an important criterion. REAL also discriminated between histologic grade and clinical aggressiveness of the disease itself. As a result of this work, retrospective studies show an increase in intraobserver and interobserver reproducibility.[9] This increased precision allows enhanced diagnostic accuracy.

The World Health Organization (WHO) classification for lymphoid disorders is based in part on the same criteria as the REAL plan. It differs from the REAL in that, since 1994, there have been new data generated concerning lymphoma and leukemia that have caused additional testing and understanding to be incorporated into the scheme.

Thus, there was an inconsistent nomenclature across the hematopoietic neoplasms with lymphomas being diagnosed through immunophenotyping, acute myelogenous leukemia (AML) by cytochemistry results, chronic myelogenous leukemia (CML) by cytogenetics, and chronic lymphocytic leukemia (CLL) by morphology.

WHO PROCESS

In 1995, the European Association of Pathologists and the International Society for Hematopathology developed a process to unite the classification process for hematopoietic neoplasms. Ten different committees of pathologists developed an initial list and definition of disease entities while multiple advisory committees of clinicians reviewed the proposed nomenclature to ensure that the classification was useful. Across all diseases, the classification is based on morphology, immunophenotyping, genetic features (karyotyping and/or molecular testing), and clinical features. Replicate iterations were used to gain consensus.

Myeloid Neoplasms

At the topmost level, all hematopoietic diseases fall into one of the following categories: myeloid, lymphoid, mast cell, and histiocytic neoplasms. Myeloid neoplasms are further discriminated into four categories: acute myeloid leukemia, myelodysplastic syndromes, myelodysplastic/myeloproliferative diseases, and myeloproliferative diseases. Myeloid neoplasms will be discussed in this article and lymphoid neoplasms in the following article.

Acute myeloid leukemia

The work on the classification of acute myeloid leukemia concentrated on answering several fundamental questions concerning the definition and sub-categorization of acute myeloid leukemia.[10] Traditionally, acute myeloid leukemia diagnosis required that the bone marrow specimen contained 30% or greater myeloblasts. Refractory anemia with excess blasts and refractory anemia with excess blasts in transformation filled in the spaces between a normal number of myeloblasts and frank leukemia. One question to be answered was: Should the number of blasts be kept at 30% or lowered and, if lowered, to what level? The decision of the groups was to lower the number of blasts to 20%. This decision, in turn, eliminated the myelodysplastic syndrome category of refractory anemia with excess blasts in transformation. The committee determined that lowering the blast count to 20% provides a clearer representation of the entity AML and eliminates the need for the myelodysplastic category, refractory anemia with excess blasts in transformation.

A second question to be answered was: should cytogenetic/molecular categories be recognized as distinct diseases? Several AML presentations are associated with specific morphology, distinctive clinical course, and identifiable chromosomal abnormalities. Unfortunately, these presentations are not strong enough to assure consistent diagnosis. With one exception (AML-M3), these genetic features do not correlate well with the established FAB classification. There is an ongoing attempt to refine the morphologic criteria that would support genetic testing. Consequently, acute myeloid leukemias with defined cytogenetic anomalies will be grouped as a single entity. This decision also allows for the inclusion of presentations of cytogenetic anomalies with low blast counts to be placed into the Acute Myelogenous Leukemia (AML) category and not the Myelodysplastic Syndromes.

A third question asked was: Should multi-lineage dysplasia, prior myelodysplastic syndromes (MDS) and/or prior therapy, be included in the classification of AML? One connecting aspect is that all of these presentations are associated with poor prognosis. Multilineage dysplasia is defined as the presence of abnormal features in cells of two or more lines. AML because of the conversion of a prior MDS leading to eventual conversion to AML and prior alkylating therapy reflect similar genetics disorders although, again, these abnormalities are not consistent enough for strong association. However, these anomalies may suggest a common pathogenesis for these three presentations.

The last question was: Should refractory cytopenia with multilineage dysplasia be considered a separate category? MDSs are clonal stem cell disorders as is AML and, at least in two separate situations (RAEB-t and AML with a history of MDS), were determined to fit in the new AML categorization. However, because there is ineffective hematopoiesis rather than suppression, a peripheral blood cytopenia, a variably hypercellular marrow and poor chemotherapeutic response, it was determined that these conditions merited their own category and will be discussed under MDS.

Table 4. FAB classificatios compared to WHO classification of acute myeloid leukemia.

FAB classification
Acute myeloid leukemias
M0 through M7

WHO classification
Acute myeloid leukemias
Acute myeloid leukemias with recurrent cytogenetic translocations
- AML with t(8;22)(q22;q22) AML1 (CBFα)/ET
- Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RARα)
- AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFβ/MYH11)
- AML with 11q23 abnormalities

Acute myeloid leukemia with multi-lineage dysplasia
- with prior myelodysplastic syndrome
- without prior myelodysplastic syndrome

Acute myeloid leukemia and myelodysplasia, therapy related
- alkylating agent related
- epipodophyllotoxin related (some may be lymphoid)
- other types

Acute myeloid leukemia, not otherwise categorized
- AML minimally differentiated
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monocytic leukemia
- Acute erythroid leukemia
- Acute megakaryocytic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Acute biphenotypic leukemia

SUMMARY OF WHO CLASSIFICATION OF AML[11] (Table 4)
The four major categories in the WHO system are:
1. Acute myeloid leukemia with recurrent genetic abnormalities
2. Acute myeloid leukemia with multilineage dysplasia
3. Acute myeloid leukemia, therapy related
4. Acute myeloid leukemia, not otherwise categorized

AML with recurrent genetic abnormalities
Acute myeloid leukemia with t(8:21)(q22;q22)(AML1/ETO) generally shows some maturation of the neutrophilic line. It occurs primarily in younger patients. This translocation accounts for about one third of karyotypically abnormal cases of AML with maturation. The peripheral blood morphology includes large blasts with abundant cytoplasm, as well as some smaller blasts. Auer rods are often present. In the bone marrow, promyelocytes, myelocytes, and mature neutrophils with variable dysplasisa are observed. Although eosinophil precursors may be increased, they do not exhibit the cytologic or cytochemical abnormalities characteristic of chromosome 16 seen in acute myelomonocytic leukemia.

Treatment with high dose cytarabine usually yields a good response with a high remission rate and long-term disease free survival, although the development of secondary karyotypic abnormalities has an adverse effect.

AML with inv(16)(p13q22) or t(16;16)(p13;q22)(CBFβ/MYH11) usually has both monocytic and granulocytic differentiation; an abnormal eosinophilic component is present in the marrow. This combination is referred to as AMML Eo.

This abnormality of chromosome 16 is found in approximately 10% to 12% of all cases of AML. Although this leukemia may occur in all age groups, it is predominately a disease of younger patients. The peripheral blood is characteristic for AMML, without an increase in eosinophils. The bone marrow has the morphological features of myelomonocytic leukemia, in addition to a variable number of eosinophils at all stages of maturation. There does not appear to be a maturation arrest; however, in the immature eosinophils the granules are usually larger than those normally present for stage and may be purple-violet in color. The granules sometimes obscure the nucleus. Naphthol ASD-chloroacetate esterase, normally negative in eosinophils, is faintly positive in these abnormal eosinophils. Auer rods may be present. Occasional cases of inv(16)(p13q22) lack eosinophils, or have only myeloid or monocytic differentiation.

Treatment with high dose cytarabine in the consolidation phase generally provides complete remission.

Acute promyelocytic leukemia (APL) with t(15;17)(q22;q12); PML/RARα exhibits promyelocytic predominance. There are two types: granular or typical APL and a microgranular variant. APL comprises 5% to 8% of all AML and most patients are middle–aged adults. Both typical and atypical APL are frequently associated with disseminated intravascular coagulation (DIC), which may be life threatening. In contrast to typical APL, the microgranular variant has a very high WBC count with rapid doubling time.

The abnormal promyelocytes of hypergranular APL show irregular size and shape. The nucleus may be kidney-shaped or bi-lobed and

the cytoplasm is filled with densely packed primary granules. The bright pink, red, or purple granules may obscure the nucleus. Bundles of Auer rods ('faggot cells') may be observed. The microgranular variant has a bi-lobed nucleus, which may resemble a butterfly. Cells are characterized by the paucity or absence of granules.

The retinoic acid receptor (RARAα) gene on 17q12 fuses with a nuclear regulatory factor on 15q22 (PML gene), resulting in the gene fusion product PML-RARα. These cells are particularly sensitive to treatment with all trans retinoic acid (ATRA), which acts as a differentiating agent. The prognosis for patients treated with ATRA and an anthracycline is relatively good.

Acute myeloid leukemia with 11q23 (MLL) abnormalities usually exhibits monocytic features. About 5% to 6% of AML cases have this abnormality. There is a predilection for children, although cases may occur at any age. Two sub-groups have a higher frequency of the 11q23 aberration: one is AML in infants and the other is therapy related leukemia, usually following treatment with DNA topoisomerase II inhibitors. Patients often present with DIC and may have extramedullary monocytic sarcomas and/or tissue infiltration (gums, skin). A strong association exists between acute leukemias with a monocytic component and deletions/translocations of 11q23. Monoblasts and promonocytes predominate. Cytoplasm may be moderately to intensely basophilic and pseudopods are common. Patients have an intermediate survival.

Acute myeloid leukemia with multi-lineage dysplasia

By definition, AML with multi-lineage dysplasia is an acute leukemia with ≥20% blasts in blood or bone marrow and at least 50% dysplasia in two or more myeloid cell lines. Usually one of the lines involved is megakaryocytic. This disorder may occur de novo or following MDS or MDS/MPD. If it is preceded by MDS, the designation should reflect that fact, i.e., 'AML evolving from MDS'. As in all morphologic observations, well-made and appropriately stained pre-treatment blood or bone marrow smears should be used for diagnosis. Dysplasia must be present in ≥50% of at least two cell lines. Some features may be more easily observed on peripheral blood smears than in bone marrow. Morphologic evidence of dysmyelopoiesis includes hypogranular neutrophils, hyposegmentation and bizarre nuclei. Dsyerythropoiesis is characterized by megaloblastic nuclei, multinucleation, bizarre nuclei, nuclear fragments, ringed sideroblasts, and PAS positivity. Micromegakaryocytes and megakaryocytes with mono-lobed or multiple separate nuclei are features of dysmegakaryopoiesis. Acute erythroleukemia and AML with maturation should be included in the differential diagnosis.

Many of the chromosomal abnormalities are similar to those found in MDS, i.e., gain or loss of chromosomes or parts of chromosomes, although translocations are less often seen. Multilineage dysplasia carries an unfavorable probability of achieving complete remission.

Acute myeloid leukemia and myelodysplastic syndromes, therapy related

Therapy related AML and MDS develop following radiation therapy and/or chemotherapy, especially with topoisomerase II inhibitors or alkylating agents. These disorders can be classified in the appropriate morphologic or genetic category with the qualifier 'therapy related'. With alkylating agents or radiation, therapy related disorders usually occur five to six years following exposure to the agent. The risk of occurrence is dependent on the age of the patient and the cumulative dose.

The process often presents as MDS with evidence of bone marrow failure, i.e., isolated cytopenia or pancytopenia with myelodysplastic changes. Frank dysplasia in multiple cell lines follows and the blast count is usually less than 5%. About two-thirds of the cases in the MDS phase fit the criteria for refractory anemia with multi-lineage dysplasia and a third of these cases have greater than 15% ringed sideroblasts. About 25% of cases fulfill the criteria for RAEB. The MDS phase may evolve to a higher grade MDS or to acute leukemia. Many patients die in the MDS phase. Karyotypic abnormalities usually involve unbalanced translocations or deletions involving chromosomes 5 and/or 7. Complex chromosomal abnormalities are common.

The morphologic changes usually affect all myeloid cell lines. Increased basophils are present in some patients. Response to antileukemic drugs is poor and survival is short.

AML following topoisomerase II inhibitor may develop relatively quickly following treatment with the causative agent with a median time of 33 to 34 months. Drugs that have been implicated include epipodophyllotoxins, etoposide, and teniposide. Anthracyclines and doxirubicin have also been implicated. Usually the development of the leukemia is not preceded by a myelodysplastic phase. Typically topoisomerase II inhibitor–related leukemia has a strong monocytic component, although some cases with granulocytic differentiation have been observed, as well as promyelocytic and even lymphocytic. Preliminary data suggest that patients will respond as they would to de novo leukemias of the corresponding morphologic type, although there has not been sufficient time for long term follow-up.

AML not otherwise categorized

Many of the leukemias in this category are synonymous with those of the FAB classification, i.e., M0 through M7 with the exception of M3 that is included in the recurrent cytogenetic translocation category. However, under the WHO classification the percentage of blasts required for the diagnosis of acute leukemias is ≥20%. The FAB classification has been well addressed in previous articles (Table 1).[2] All these subtypes are treated similarly. Additional leukemias in this category include acute basophilic leukemia, acute panmyelosis with myelofibrosis, and myeloid sarcoma.

In acute basophilic leukemia, the primary differentiation is basophilic. This is a fairly rare disorder, comprising less than 1% of all cases of AML. Patients present with the usual features of bone marrow failure and there may or may not be circulating blasts. Organomegaly, cutaneous involvement, and lytic lesions may be present. Additionally, symptoms related to hyperhistaminemia may be present.

Blasts are medium in size with a high nuclear/cytoplasmic ratio. The nucleus is oval, round, or bi-lobed with one to three prominent nucleoli. The moderately basophilic cytoplasm contains a variable number of coarse granules; cytoplasmic vacuoles may be present. Metachromatic positivity with tolidine blue is characteristic. Blasts often appear negative for Sudan Black B, myeloperoxidase, and non-specific esterase, but by electron microscopy peroxidase may be detected. No consistent chromosome aberrations have been identified in basophilic leukemia. This is such a rare leukemia that very little data on survival is available, although in the cases described, survival has been very short.

Acute panmyelosis with myelofibrosis is an acute panmyeloid proliferation with fibrosis of the bone marrow. It is also called acute myelofibrosis, myelosclerosis, and acute myelodysplasia with myelofibrosis. It is a very rare disorder which occurs primarily in adults and may occur de novo or as a result of treatment with an alkylating agent and/or radiation. Patients present with weakness and fatigue, marked pancytopenia, and little to no splenomegaly. The disease is rapidly progressive.

Myeloid sarcoma is a tumor mass of myeloblasts or immature myeloid cells occurring in bone or in an extramedullary site. It is sometimes called granulocytic sarcoma or chloroma. Myeloid sarcomas may be the first evidence of AML. The most common type of myeloid sarcoma is the granulocytic type, composed of myeloblasts, neutrophils, and neutrophil precursors. It must be differentiated from Hodgkin, Burkitt, and large cell lymphomas. Immunophenotyping or immunohistochemistry is essential. A myeloid sarcoma occurring in the setting of MDS or MPD is equivalent to blast transformation. When a sarcoma occurs outside the setting of pre-existing disease, i.e., as an isolated lesion, radiotherapy may provide a long survival.

A last category in the WHO histological classification of acute myeloid leukemias describes leukemias of ambiguous lineage and encompasses undifferentiated, bilineal and biphenotypic leukemias.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes are a heterogeneous group of clonal stem cell disorders characterized by dysplasia (single or multi-lineage), ineffective hematopoiesis, and cytopenias. They occur primarily in persons over the age of 50, less frequently in young adults and rarely in children.[12]

Although there is some evidence that an inherited form of MDS exists, the majority of cases occur as primary (de novo), or as therapy related (TR-MDS) disorders. TR-MDS occurs in patients with a history of treatment with radiotherapy and/or chemotherapy, especially with alkylating agents. Possible causes for de novo MDS include viruses, benzene, or other chemical exposure; there is an increased incidence of MDS in smokers.

The initiating defect appears to be at the level of the myeloid stem cell, but there is variable involvement of the lymphoid line, supporting the theory of pluripotential stem cell involvement.[13] Once the stem cell is mutated, it produces a clone that expands in size at the expense of the normal cell population.[14]

Apoptosis (programmed cell death) regulates cell population by decreasing cell survival. Current evidence suggests that disruption of apoptosis may be responsible for ineffective hematopoiesis in MDS and consequent cytopenias. In MDS, apoptosis appears to be increased early in the disease when cytopenias are present and decreased late in the disease when proliferation of immature cells occurs.[12, 15] Cytogenetic defects are usually characterized by structural or numeric defects, e.g., -5/5q-, -7/7q-, +8, as opposed to the balanced translocations seen in de novo AML.[16] Molecular mutations have been found, including RAS, FMS and p53. Telomerase activity is enhanced in MDS and is associated with a more aggressive course .[14,16]

Clinical Presentation

Patients usually present with fatigue, weakness, dyspnea, and other symptoms related to anemia, and occasionally with recurrent infections due to neutropenia, or bleeding related to thrombocytopenia. Splenomegaly is an infrequent finding, and hepatomegaly is rare.

Each of the myeloid cells lines has dyspoietic features, which vary according to the degree of involvement. Among the common morphologic findings in dyserythropoiesis are oval macrocytes and hypochromic microcytes, creating a dimorphic population. In the bone marrow, red blood cell (RBC) precursors may contain more than one nucleus, exhibit abnormal nuclear shapes, uneven cytoplasmic staining and there may be ringed sideroblasts. Dysmyelopoietic features include uneven persistent basophilic cytoplasm, uneven cytoplasmic staining, abnormal granulation, and abnormal nuclear shapes. On the peripheral smear there may be giant platelets or platelets with uneven granulation. Circulating micromegakaryocytes may be found. The bone marrow may exhibit large mononuclear megakaryocytes and abnormal nuclear shapes.

The cells produced by abnormal maturation have not only morphologic variations, but may also have abnormal function, such as decreased chemotaxis, deficient phagocytosis, impaired microbicidal activity, shortened lifespan, and impaired platelet activity.

Classification
In 1982, the FAB group classified MDS based primarily on morphology in peripheral blood and bone marrow. With the exception of refractory anemia with ringed sideroblasts (RARS) and CMML, the major distinction between sub-types was the percentage of blasts in the bone marrow. CMML was defined by the absolute monocyte count, and RARS by the percentage of ringed sideroblasts (Table 2). Although some criteria of the FAB classification remain essentially the same with the WHO classification, there are several substantial differences. One of these is the consideration of CMML. Since CMML has both dsyplastic and proliferative components, it did not fit well into either MDS or MPD classifications. Thus, WHO created a category of MPD/MDS, which will be discussed later in this article.

Another substantial difference between FAB and WHO classifications is the percentage of blasts required to distinguish MDS from AML. Multi-lineage dysplasia as seen in RAEB progresses to either bone marrow failure or frank acute leukemia, thus, the prior category of RAEBt (20% to 29% blasts) is moved into the WHO AML category (>20% blasts) as is any low blast count leukemic presentation that shows one of the AML type cytogenetic abnormalities.

Refractory anemia (RA) and RARS are erythroid dysplasias. Both of these presentations are similar enough to be considered as a single category by WHO.

An additional category was added to append the 5q- syndrome because of its distinctive morphologic and clinical features.[10] Some members of the International MDS Study Group do not agree with all the proposals of the WHO and have recorded their concerns.[17]

Summary of WHO Classification of MDS[10,11,16] (Table 5)
The major categories in the WHO system are:
1. Refractory anemia, with or without ringed sideroblasts
2. Refractory cytopenia with multilineage dysplasia
3. Refractory anemia with excess blasts
4. 5q- syndrome
5. Myelodysplastic syndrome, unclassifiable

RA with or without ringed sideroblasts: The classification of this group is essentially the same as in the FAB classification and has been covered elsewhere.[13,14,18]

Refractory cytopenia with multilineage dysplasia (RCMD): By definition, RCMD exhibits bi-cytopenia or pancytopenia and dysplastic changes in 10% of two or more of the myeloid cell lines. There are fewer than 1% blasts in the peripheral blood and less than 5% in the bone marrow. Monocytes are less than 1 x 10^9/L and no Auer rods are seen. Clonal chromosome abnormalities may be seen in up to 50% of patients with RCMD, including +8, -7, 7q-, -5, 5q- and 20q-. Complex karyotypes are common. Survival is related to the degree of cytopenias and dysplasia, with a mean of 33 months. Those with complex karyotypes have a poorer survival, similar to that of RAEB.[11,16]

Refractory anemia with excess blasts (RAEB): This category is essentially the same as the FAB classification and has been reviewed elsewhere.[13,14,18]

5q- Syndrome: This is a distinct subtype of MDS associated with the isolated deletion between bands 31 and 33 on chromosome 5. It is important to note that if any additional cytogenetic abnormalities are present, the case should not be classified as 5q-. There is a prevalence for females, from middle age to elderly. Distinctive morphologic characteristics include marked macrocytosis, large mononuclear megakaryocytes, and occasional thrombocytosis. This subtype carries a good prognosis with relatively long survival.

Myelodysplastic syndrome, unclassifiable: This term is reserved for cases of MDS that do not fit the criteria for other categories. Blasts are not increased in blood or bone marrow.

Treatment
MDS is such a heterogeneous disorder that there is no one 'standard' treatment. Management may include 'watch and wait', supportive care, chemotherapy, differentiating agents and growth factors, or bone marrow transplantation. Currently only bone marrow transplant is considered a cure. However, as research concerning the role of apoptosis in MDS continues, future therapies might be aimed at controlling apoptosis, either as single agents or in combination with chemotherapeutic drugs.[15]

MYELOPROLIFERATIVE DISORDERS

As with the other conditions mentioned, myeloproliferative dis-

Table 5. FAB classification compared to WHO classification of myelodysplastic syndromes

FAB classification
Refractory anemia
Refractory anemia with ringed sideroblasts
Refractory anemia with excess blasts
Refractory anemia with excess blasts in transformation
WHO classification
Refractory anemia with or without ringed sideroblasts
Refractory cytopenia with multi-lineage dysplasia
Refractory anemia with excess blasts
5q- Syndrome
Myelodysplastic syndrome, unclassifiable

eases (MPD) are clonal stem cell problems. They are typically described as having 'effective' hematopoiesis in that they result in elevated numbers of one or more cell lines. Occasionally there is hepatosplenomegaly, marrow hypercellularity with normal maturation, and no dysplastic changes.

Eventually perhaps the classification of the MPD will be based on molecular pathology. At the present time that knowledge is not yet available, so that the classification is based on the lineage of the proliferating cell, prominence of marrow fibrosis, along with a combination of blood and bone marrow findings. Accepted into this category without controversy are polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis, and Philadelphia chromosome positive chronic myelogenous leukemia (CML). Of concern was the placement of the other chronic myelogenous leukemias - juvenile chronic myelomonocytic leukemia (JMML), chronic myelomonocytic leukemia (CMML), and atypical CML (aCML). Another concern is the fine line between myeloproliferative syndromes and myelodysplastic syndromes. Should there be only one category for each or should there be an additional mixed category? There was sufficient disagreement between the committees that a combination category of myeloproliferative and myelodysplastic syndromes, which is discussed later in this article, was created.

In addition to the traditional entities of PV, ET, chronic idiopathic myelofibrosis (CIMF), and Philadelphia chromosome positive CML, the WHO designated chronic neutrophilic leukemia, chronic eosinophilic leukemia (hypereosinophilic syndrome), and MPD, unclassified (Table 6).

Chronic neutrophilic leukemia (CNL)[11]

CNL is rarely seen and can be determined only after other causes of reactive neutrophilia and other MPDs have been excluded. It is characterized by sustained peripheral blood neutrophilia, neutrophilic expansion in the hypercellular bone marrow, and hepatosplenomegaly. No Philadelphia chromosome or BCR/ABL fusion gene is present. The WBC count is 25.0 x 10^9/L or greater. Segmented neutrophils predominate, but there may also be an increase in bands. Less mature cells are only rarely seen in the peripheral blood (<5% of differential). Neutrophils often have toxic granulation, but have no dysplastic features. In the bone marrow the percentages of myelocytes and neutrophils are increased but blasts and promyelocytes are not. In CNL, the leukocyte alkaline phosphatase score is increased, as opposed to the low value seen in Ph chromosome positive CML. CNL is usually a slowly progressive disorder, but it may transform to an acute leukemia in some cases.

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

Requirements for diagnosis of CEL include persistent eosinophilia ≥1.5 x 10^9/L, increased bone marrow eosinophils and fewer than 20% myeloblasts in blood or bone marrow. All causes of reactive eosinophilia must be ruled out, as well as neoplastic disorders with secondary eosinophilia. CEL and HES involve both blood and bone marrow, as well as infiltration into tissues. The release of cytokines and humoral factors from eosinophils damages organs, especially the heart, lung, CNS, skin and GI tract. Hepatosplenomegaly is common. No specific chromosomal or molecular abnormalities are seen. If the Philadelphia chromosome or BCR/ABL fusion gene is present, the disease should be diagnosed as CML.

Chronic myeloproliferative disease, unclassifiable

This designation should be reserved for cases that have definite clinical, laboratory, and morphologic features of MPD, but do not fit the criteria for a specific category. There is no Ph chromosome or BCR/ABL fusion gene. Many of these cases are patients in the very early stages of MPD, or in the very late fibrotic stages, when the more aggressive disease obscures the underlying disorder.

Myeloproliferative/myelodysplastic syndromes (MPD/MDS)[10,11] **(Table 7)**

One question that led to this new category was where CMML could or should be divided into the subcategories of MDS and MPD. CMML has long been difficult to classify in that it presents with features of both myeloproliferation and dysplasia. Many patients present with absolute neutrophil values of decreased to within reference range. There is multi-lineage dyspla-

Table 6. FAB classification compared to WHO classification of myeloproliferative syndromes

FAB classification	WHO classification
Polycythemia vera	Polycythemia vera
Essential thrombocythemia	Essential thrombocythemia
Myelofibrosis	Chronic idiopathic myelofibrosis
Chronic myelogenous leukemia	Chronic myelogenous leukemia, Philadelphia chromosome (ph)[t(9;22)(qq34;q11), BCR/ABL]+
	Chronic neutrophilic leukemia
	Chronic eosinophilic leukemia/hypereosinophilic syndrome

sia and the marrow morphology resembles RAEB with monocytosis. Other patients present with severe splenomegaly, significant neutrophilia, and monocytosis. As there are currently no definitive differences in cytogenetics, oncogene mutations, or clinical outcomes seen in these two presentations, it was determined that they are one disease. A secondary issue of placement was finally settled by the creating of a new subcategory of myeloproliferative/myelodysplastic syndromes. Also in this group are atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, and MDS/MPD, unclassifiable.

Atypical CML (aCML) was first recognized as a disease involving proliferation and dysplastic changes. It is always Philadelphia chromosome negative and has a noticeably worse prognosis in a shortened timeframe. It is easily differentiated from Philadelphia chromosome positive CML through both cytogenetic testing and morphology. The name, aCML, implies that there is a relationship of some sort between both diseases and a chronic process; neither of which is correct. However, no consensus was found on a substitute name and aCML remains aCML although this issue might be lessened by the placement of aCML into a subcategory separate from CML.

Juvenile myelomonocytic leukemia is similar to the adult form in that there is a persistent monocytosis, fewer than 20% blasts and promonocytes, and absence of Ph chromosome or BCR/ABL fusion gene. Additionally there must at least two of the following: increased hemoglobin F for age, immature granulocytes in the peripheral blood, WBC greater than 10 x 10^9/L, clonal chromosomal abnormality, e.g., 30% to 40% have monosomy 7, and GM-CSF of myeloid progenitors in vitro. The prognosis of JMML is overall poor and many children die from organ failure. Bone marrow transplant is the only therapy to experience much success.

CONCLUSIONS

This approach to the classification of hematologic malignancies represents the first time that a consistent approach to classification has been attempted. It uses the most current testing protocols available and relies on a more broad approach to disease conceptualization. The subcategory 'unclassified' leaves room for identifying new entities and for incorporating new criteria, new testing protocols, and new disease definitions. One concern, as with any new structure, is the need for a mechanism for correction and updating. Change is never easy and the shorthand methods of referring to diseases by abbreviation may be difficult to leave but this classification may provide more clarity and better patient care.

Table 7. FAB classification compared to WHO classification of myelodysplastic/-myeloproliferative syndromes

FAB Classification	**WHO Classification**
Not applicable	Chronic myelomonocytic leukemia (CMML)
	Atypical chronic myelogenous leukemia (aCML) (negative for Philadelphia chromosome)
	Juvenile myelogenous/myelomonocytic leukemia (JMML)

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