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Classification of acute myeloid leukemia

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Abstract

The World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues was revised in 2017 on the basis of recent high-throughput sequencing and gene expression data on hematologic malignancies. This review explores the current WHO classification of acute myeloid leukemia (AML) and related precursor neoplasms, highlighting the changes made in the current edition and focusing on the diagnosis of AML.

Key Words Acute myeloid leukemia, Classification, Diagnosis

INTRODUCTION

Acute myeloid leukemia (AML) comprises a heterogeneous group of neoplastic disorders in which ≥20% of cells in the blood or bone marrow are myeloblasts. Historically, AML has been classified according to the morphology and immunophenotype but since the 3rd edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues, genetic abnormalities have been incorporated in the diagnostic algorithms for AML [1, 2]. Recurrent genetic abnormalities include chromosomal translocations involving transcription factors associated with distinct clinical, morphological, and immunophenotypic features that define a clinicopathological and genetic entity. In the revised 4th edition of the WHO classification published in 2017 [3], AML is classified into 6 categories: AML with recurrent genetic abnormalities; AML with myelodysplasia-related changes (MRC); therapy-related myeloid neoplasms (t-MN); AML, not otherwise specified (NOS); myeloid sarcoma; and myeloid proliferations related to Down syndrome (DS) (Table 1). This review discusses each of these categories and highlights the initial diagnostic workup necessary for their diagnosis.

AML with recurrent genetic abnormalities

This entity includes AML with balanced translocation/inversions, as well as AML with gene mutations, and accounts for about 20–30% of patients with AML. AML with balanced translocations include t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*, *PML-RARA*, t(9;11)(p21.3;q23.3); *KMT2A-MLLT3*, t(6;9)(p23;q34.1); *DEK-NUP214*; inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*, t(1;22)(p13.3;q13.1); *RBM15-MKL1*; and (provisional entity) AML with *BCR-ABL1*. Many of these disease categories have characteristic morphological and immunophenotypic features. Of these categories, if *PML-RARA* and inv(16)(p13.1q22) or t(16;16) are present with t(8;21), AML can be diagnosed regardless of the blast count [3]. AML with *BCR-ABL1* is a newly introduced provisional entity that was included separately despite low incidence because its characteristics are different from the blast phase of chronic myeloid leukemia [4] and is an aggressive disease. Moreover, studies have shown that patients with this form of AML might benefit from tyrosine kinase therapy [5, 6].

AML with gene mutations is another category under AML with recurrent genetic abnormalities. AML with mutated *NPM1* and biallelic *CEBPA* have been incorporated into the "AML with recurrent genetic abnormalities" entity, and AML with *RUNX1* mutation was added as a new provisional entity. AML with *NPM1* mutation is the most recurrent genetic mutation in AML and is usually associated with a normal karyotype [7]. *NPM1*-mutated AML shows good

Table 1. World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia.

WHO classification of myeloid neoplasms and acute leukemia
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22q22.1); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *KMT2A-MLLT3*
AML with t(6;9)(p23;q34.1); *DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*
Provisional entity: *AML with BCR-ABL1*
AML with mutated *NPM1*
AML with biallelic mutation of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified (NOS)
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations associated with Down syndrome
Transient abnormal myelopoiesis (TAM) associated with Down syndrome
Myeloid leukemia associated with Down syndrome

Table 2. Cytogenetic abnormalities diagnostic of acute myeloid leukemia with myelodysplasia-related changes [3].

Type of cytogenetic abnormality	Karyotype
Complex karyotype	3 or more abnormalities
Unbalanced abnormalities	−7/del(7q) del(5q)/t(5q) i(17q)/t(17p) −13/del(13q) del(11q) del(12p)/t(12p) idic(X)(q13)
Balanced abnormalities	t(11;16)(q23.3;p13.3) t(3;21)(q26.2;q22.1) t(1;3)(p36.3;q21.2) t(2;11)(p21;q23.3) t(5;12)(q32;p13.2) t(5;7)(q32;q11.2) t(5;17)(q32;p13.2) t(5;10)(q32;q21) t(3;5)(q25.3;q35.1)

prognosis, but accompanying *FLT3*-ITD mutations may alter the prognosis [8, 9]. In the revised classification, only those with biallelic *CEBPA* mutation are included as a separate entity owing to its beneficial effect on prognosis [10, 11]. AML with mutated *RUNX1* has been incorporated in to the AML classification and is known to have poor prognosis [12, 13]. However, a diagnosis of *RUNX1*-mutated AML should not be made for cases that fulfil the criteria for other specific AML subtypes, including AML-MRC, t-MN, or AML with recurrent genetic abnormalities. Most *RUNX1* mutations are monoallelic, and the mutations are commonly frameshift or missense without any hotspots [14]. Although AML with *FLT3* mutations are frequently present, it is not separately assigned as an entity due to its presence in many AML subtypes. Nevertheless, owing to their therapeutic [15] and prognostic significance [16], testing for *FLT3* mutations must be carried out in all patients with AML [8, 9].

AML with myelodysplasia related changes

The diagnosis of AML-MRC requires that the following criteria are met. First, the blast count in blood or marrow should be ≥20%; second, patients should have a history of myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (MPN), or MDS-related cytogenetic abnormality (Table 2) or multilineage dysplasia; and third, patients should not have received prior cytotoxic or radiation therapy for an unrelated disease or have the recurrent cytogenetic abnormalities described for AML with recurrent genetic abnormalities. AML-MRC generally has a poor prognosis with a lower rate of complete remission than other AML subtypes [17, 18]. To diagnose AML-MRC based on morphology, dysplasia must be present in ≥50% of cells in at least two hematopoietic cell lines. Moreover, multilineage dysplasia alone is insufficient to diagnose AML-MRC in a de novo case of AML with mutated *NPM1* or biallelic mutations of *CEBPA*, as the prognosis is not different regardless of the presence of multilineage dysplasia in these subtypes [19, 20]. Deletion (9q) has been removed from the MDS-related cytogenetic abnormalities that are now used to define AML-MRC owing to the association with *NPM1* or biallelic *CEBPA* mutations [21, 22].

Therapy-related myeloid neoplasm

t-MN includes t-AML, t-MDS, t-MDS/MPN, which occur as a complication of cytotoxic therapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorder. Cytotoxic agents implicated in t-MN include alkylating agents, topoisomerase II inhibitors, some antimetabolites, anti-tubulin agents, and radiation therapy. t-MN accounts for 10–20% of all cases of MDS and AML [23]. Regardless of the blast count and morphologic diagnosis, t-MDS and t-AML are included as t-MN, owing to the presence of prior iatrogenic exposure to mutagenic agents and its relation to pathogenesis of the t-MN, although recent studies have suggested some inherited risk factors [24, 25]. The prognosis of t-MN is generally poor, influenced by cyto-

genetic and genetic mutations, as well as the underlying malignancy for which prior therapy was received [26, 27].

Acute myeloid leukemia, not otherwise specified

Cases of AML that are not classified into any of the above-mentioned categories are classified as AML, NOS. This category classifies AML based on morphology, cytochemistry, and immunophenotype, which was the basis for earlier AML classifications [1, 2]. Subcategories include AML with minimal differentiation, without maturation, with maturation, acute myelomonocytic leukemia, acute monoblastic and monocytic leukemia, pure erythroid leukemia, acute megakaryoblastic leukemia, acute basophilic leukemia, and acute panmyelosis with myelofibrosis. Changes have been made for erythroid leukemia and bone marrow with >80% immature erythroid precursors; bone marrow nucleated cells with >30% proerythroblasts is only included in the pure erythroid leukemia category and thus, the myeloblast counts are <20% [28]. Cases previously classified as erythroleukemia (myeloid/erythroid) are now classified as MDS according to the blast count, cytopenia, and dysplasia, because they share greater similarity with MDS than with AML [29, 30].

Myeloid sarcoma

A tumor mass consisting of myeloid blasts, occurring at a site other than the bone marrow, is diagnosed as myeloid sarcoma. The diagnosis is equivalent to a diagnosis of AML and can precede or coincide with AML [31, 32]. Myeloid sarcoma shows blastic-type as well as monoblastic or myelomonocytic type [31]; recent studies using next-generation sequencing have identified mutations similar to those implicated in AML, such as *KIT* or *FLT3* mutations [33].

Myeloid proliferations associated with Down syndrome

Individuals with DS are known to have increased risk of leukemia [34, 35]. Transient abnormal myelopoiesis (TAM) associated with DS and myeloid leukemia associated with DS are included in this category. TAM is a disorder of newborns with DS that presents with clinical and morphological findings of AML at 3–7 days after birth [36]. Most patients exhibit spontaneous remission but others develop AML after 1–3 years. Most cases of myeloid leukemia associated with DS are acute megakaryoblastic leukemia [37]. In individuals with DS, the distinction between MDS and AML is irrelevant; thus, both are included in the category of myeloid leukemia associated with DS. In addition to trisomy 21, mutations of *GATA1* are pathognomonic of this category [38]. These children should be treated based on DS-specific protocols [39].

CONCLUSION

Diagnosis of AML according to the revised WHO classification [3] requires the results of morphological, immunophenotypic, cytogenetic, and molecular genetic testing, as well as prior medical history and clinical information. For adult patients with AML, cytogenetic and molecular genetic testing results are needed to assign AML to the recurrent genetic abnormalities category. Cytogenetic studies, screening for gene rearrangements, and assessment of gene panels including *NPM1, CEBPA, RUNX1* are currently required for classification. The medical history or prior therapy history is necessary to assign AML to t-MN or AML-MRC. If patients are not assigned to any one of these prior categories, a diagnosis of AML, NOS is made based on the morphology and immunophenotype. In individuals with DS, myeloid proliferations related to DS should be considered. Recent molecular genetic findings will further enrich our understanding of AML and are expected to be incorporated into future classifications.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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