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The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues: An overview with emphasis on the myeloid neoplasms

James W. Vardiman*

University of Chicago Medical Center, 5841 South Maryland Avenue, MC0008, Chicago, IL 60637, United States

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ABSTRACT

The World Health Organization (WHO) classification of myeloid and lymphoid neoplasms utilizes morphology, immunophenotype, genetics and clinical features to define disease entities of clinical significance. It is a consensus classification in which a number of experts have agreed on the classification and diagnostic criteria. In general, the classification stratifies neoplasms according to their lineage (myeloid, lymphoid, histiocytic/dendritic) and distinguishes neoplasms of precursor cells from those comprised of functionally mature cells. Lymphoid neoplasms are derived from cells that frequently have features that recapitulate stages of normal B-, T-, and NK-cell differentiation and function, so to some extent they can be classified according to the corresponding normal counterpart, although additional features, such as genotype, clinical features and even location of the tumor figure into the final classification listing as well. Five major subgroups of myeloid neoplasms are recognized based mainly on their degree of maturation and biologic properties: myeloproliferative neoplasms (MPNs) which are comprised primarily of mature cells with effective proliferation; myeloid (and lymphoid) neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1*, defined largely by the finding of significant eosinophilia and specific genetic abnormalities; myelodysplastic/myeloproliferative neoplasms (MDS/MPN), comprised mainly of mature cells with both effective and ineffective proliferation of various lineages; myelodysplastic syndromes (MDS), in which immature and mature cells are found with abnormal, dysplastic and ineffective maturation, and acute myeloid leukemia (AML), comprised of precursor cells with impaired maturation. Genetic abnormalities play an important role as diagnostic criteria for further subclassification of some myeloid neoplasms, particularly of AML. Although therapy-related MDS and AML (t-MDS/AML) often have genetic defects identical to those found in de novo AML and de novo MDS, they are classified separately from de novo AML and MDS in order to emphasize their unique clinical and biologic properties.

1. Introduction and background

An ideal classification scheme of hematopoietic malignancies should include diseases that are clinically significant, clearly defined, mutually exclusive of each other, and that can be diagnosed using currently available technology and information. In addition, there should be general consensus and acceptance of the classification for it to be useful for daily clinical practice as well as for scientific investigations. Lastly, the classification should be flexible and changeable as new information accumulates. In 2001, the World Health Organization (WHO), in collaboration with the Society for Hematopathology and the European Association of Hematopathology, attempted to meet these goals and published a classification of Tumors of the Hematopoietic and Lymphoid Tissues as part of the 3rd edition of the series, *WHO Classification of Tumors* [1]. In 2008, the classification was updated and published as part of the 4th edition of the WHO monograph series [2]. The aim of the revision was to incorporate new scientific and clinical information that has accumulated since the previous edition in order to refine diagnostic criteria for previously described neoplasms and to introduce newly recognized disease entities.

1.1. Principles of the WHO classification

The principles of the WHO classification have been previously described [3–5]. The major principle is that the classification relies on a combination of clinical, morphologic, immunophenotypic, genetic and other biologic features to define specific disease

* Tel.: +1 773 702 6196; fax: +1 773 702 1200.
E-mail address: James.vardiman@uchospitals.edu.

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entities—a logical approach similar to that followed by a clinician and pathologist as they work together to reach a diagnosis for a patient suspected to have a hematopoietic neoplasm. The relative contribution of each of these parameters to the final diagnosis varies depending on the disease entity. For some neoplasms, morphology alone may be sufficient for classification, but in others, knowledge of the genetic lesion is necessary for the final diagnosis and classification, and often for the treatment as well. Although perhaps overused as a prototype for the identification and classification of hematopoietic neoplasms, chronic myelogenous leukemia (CML) serves as a good example of the approach and goal of the WHO classification for an individual disease. CML is mainly recognized by its clinical and morphologic features, but is consistently associated with a specific genetic defect, the *BCR-ABL1* fusion gene, that results in the production of a constitutively activated tyrosine kinase (TK) that in turn activates a number of different cellular pathways to influence proliferation, survival and differentiation of the neoplastic cell. The protein provides a target for TK inhibitor therapy that has prolonged the lives of thousand of patients with CML [6]. However, the diagnosis of CML is not made on any single parameter—there are other disorders that can mimic its clinical presentation and morphology, and the *BCR-ABL1* gene is found in cases of acute lymphoblastic leukemia and mixed phenotype acute leukemia as well as in CML. Thus, CML is an excellent example of the integration of all pieces of relevant information into the definition of a disease entity.

A second principle of the classification is that there should be agreement on the diagnostic criteria, nomenclature and classification among a number of experts in the field. Key to the development of the 4th edition was the input of approximately 70 internationally recognized clinicians and clinical scientists who met with the pathologists to discuss the merits of the proposed classification scheme and the revisions. Eventually, over 150 hematopathologists, clinical hematologists and scientists participated in the final development and writing of the 4th edition of the *WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues*.

2. The WHO classification of hematopoietic and lymphoid tumors, general features

The complete WHO classification is listed in Table 1. Perusal of the table reveals that the hematopoietic neoplasms are stratified broadly according to the lineage of the neoplastic cells, i.e., myeloid, lymphoid, histiocytic/dendritic, or ambiguous lineage. The latter category is comprised of precursor cell neoplasms (acute leukemia) that are comprised of cells that lack any specific lineage-associated markers and are thus "undifferentiated," or that express antigens of more than one lineage, and thus appear to have a mixed lineage phenotype [7,8]. Neoplasms comprised of precursor cells (acute myeloid leukemia, lymphoblastic leukemia/lymphoma, blastic plasmacytoid dendritic cell neoplasm, and acute leukemia of ambiguous lineage) are considered separately from those comprised of more mature cells (myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndromes, mature B-cell and T/NK-cell lymphoma, Hodgkin lymphoma and histiocytic/dendritic cell neoplasms). For the mature lymphoid neoplasms, further sub-classification and listing is based to some extent on the stage of differentiation as compared to a postulated normal counterpart (e.g., mantle cell lymphoma, follicular lymphoma), on morphology (e.g., diffuse large B cell lymphoma), on clinical presentations or the clinical setting (e.g., diffuse large B cell lymphoma associated with chronic inflammation), or more commonly, on the combination of morphologic, immunophenotypic and/or genetic parameters that together allow a specific disease entity to be defined (e.g., Anaplastic large cell lymphoma, ALK pos-

Table 1
WHO classification of hematopoietic and lymphoid neoplasms.

- Myeloproliferative neoplasms
  - Chronic myelogenous leukaemia, *BCR-ABL1* positive
  - Chronic neutrophilic leukaemia
  - Polycythaemia vera
  - Primary myelofibrosis
  - Essential thrombocythaemia
  - Chronic eosinophilic leukaemia, NOS
  - Mastocytosis
    - Cutaneous mastocytosis
    - Systemic mastocytosis
    - Mast cell leukaemia
    - Mast cell sarcoma
    - Extracutaneous mastocytoma
    - Myeloproliferative neoplasm, unclassifiable
- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB or FGFR1*
  - Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
  - Myeloid neoplasms with *PDGFRB* rearrangement
  - Myeloid and lymphoid neoplasms with *FGFR1* abnormalities
- Myelodysplastic/myeloproliferative neoplasms
  - Chronic myelomonocytic leukaemia
  - Atypical chronic myeloid leukaemia, *BCR-ABL1* negative
  - Juvenile myelomonocytic leukaemia
  - Myelodysplastic/myeloproliferative neoplasm, unclassifiable
  - *Refractory anaemia with ring sideroblasts associated with marked thrombocytosis*
- Myelodysplastic syndromes
  - Refractory cytopenia with unlineage dysplasia
    - Refractory anaemia
    - Refractory neutropenia
    - Refractory thrombocytopenia
  - Refractory anaemia with ring sideroblasts
  - Refractory cytopenia with multilineage dysplasia
  - Refractory anaemia with excess blasts
  - Myelodysplastic syndrome associated with isolated del(5q)
  - Myelodysplastic syndrome, unclassifiable
  - Childhood myelodysplastic syndrome
    - *Refractory cytopenia of childhood*
- Acute myeloid leukaemia (AML) and related precursor neoplasms
  - AML with recurrent genetic abnormalities
    - AML with t(8;21)(q22;q22), *RUNX1-RUNX1T1*
    - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;p22); CBFB-MYH11
    - Acute promyelocytic leukaemia with t(15;17)(q22;q12);PML-RARA
    - AML with t(9;11)(p22;q23)MLLT3-MLL
    - AML with t(6:9)(p23;q34); DEK-NUP214
    - AML with inv(3)(q21q26.2) or t(3.3)(q21;q26.2); RPN1-EVI1
    - AML (megakaryoblastic) with t(1:22)(p13;q13); RBM15-MKL1
    - AML with mutated NPM1
    - AML with mutated CEBPA
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukaemia, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukaemia
  - Acute monoblastic and monocytic leukaemia
  - Acute erythroid leukaemia
  - Acute megakaryoblastic leukaemia
  - Acute basophilic leukaemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukaemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
- Acute leukaemias of ambiguous lineage
  - Acute undifferentiated leukaemia
  - Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); *BCR-ABL1*
  - Mixed phenotype acute leukaemia with t(v;11q23); *MLL* rearranged
  - Mixed phenotype acute leukemia, B/myeloid, NOS
  - Mixed phenotype acute leukaemia, T/myeloid, NOS
  - *Natural killer (NK) cell lymphoblastic leukaemia/lymphoma*

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Table 1 (*Continued*)

- Precursor lymphoid neoplasms
  - B lymphoblastic leukaemia/lymphoma
    - B lymphoblastic leukaemia/lymphoma, NOS
    - B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
    - B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL 1*
    - B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL* rearranged
    - B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22) *TEL-AML 1 (ETV6-RUNX1)*
    - B lymphoblastic leukaemia/lymphoma with hyperdiploidy
    - B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
    - B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32) *IL 3-IGH*
    - B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PAX1*
  - T lymphoblastic leukaemia/lymphoma
- Mature B-cell neoplasms
  - Chronic lymphocytic leukaemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukaemia
  - Splenic B-cell marginal zone lymphoma
  - Hairy cell leukaemia
    - *Splenic B-cell lymphoma/leukaemia, unclassifiable*
      - *Splenic diffuse red pulp small B-cell lymphoma*
      - *Hairy cell leukaemia-Variant*
  - Lymphoplasmacytic lymphoma
    - Waldenström macroglobulinemia
  - Heavy chain diseases
    - Alpha heavy chain disease
    - Gamma heavy chain disease
    - Mu heavy chain disease
  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
  - Nodal marginal zone lymphoma
  - *Paediatric nodal marginal zone lymphoma*
  - Follicular lymphoma
  - *Paediatric follicular lymphoma*
  - Primary cutaneous follicle centre lymphoma
  - Mantle cell lymphoma
  - Diffuse large B-cell lymphoma (DLBCL), NOS
    - T-cell/histiocyte rich large B-cell lymphoma
    - Primary DLBCL of the CNS
    - Primary cutaneous DLBCL, leg-type
    - *EBV positive DLBCL of the elderly*
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - ALK positive large B-cell lymphoma
  - Plasmablastic lymphoma
  - Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
  - Primary effusion lymphoma
  - Burkitt lymphoma
  - B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
  - B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
- Mature T-cell and NK-cell neoplasms
  - T-cell prolymphocytic leukaemia
  - T-cell large granular lymphocytic leukaemia
  - *Chronic lymphoproliferative disorder of NK-cells*
  - Aggressive NK-cell leukaemia
  - Systemic EBV positive T-cell lymphoproliferative disease of childhood
  - Hydroa vacciniforme-like lymphoma
  - Adult T-cell leukaemia/lymphoma
  - Extranodal NK/T-cell lymphoma, nasal type
  - Enteropathy-associated T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Mycosis fungoides
  - Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*

Table 1 (*Continued*)

- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- *Anaplastic large cell lymphoma, ALK negative*
- Hodgkin lymphoma
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Classical Hodgkin lymphoma
    - Nodular sclerosis classical Hodgkin lymphoma
    - Mixed cellularity classical Hodgkin lymphoma
    - Lymphocyte-depleted classical Hodgkin lymphoma
- Histiocytic and dendritic cell neoplasms
  - Histiocytic sarcoma
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
  - Interdigitating dendritic cell sarcoma
  - Follicular dendritic cell sarcoma
  - Fibroblastic reticular cell tumor
  - Indeterminate dendritic cell tumor
  - Disseminated juvenile xanthogranuloma
- Post-transplant lymphoproliferative disorders (PTLD)
  - Early lesions
    - Plasmacytic hyperplasia
    - Infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD (B- and T/NK-cell types)[a]
  - Classical Hodgkin lymphoma type PTLD[a]

NOS, not otherwise specified. The italicized numbers are provisional codes for the 4th edition of ICD-O. While they are expected to be incorporated in the next ICD-O edition, they currently remain subject to changes. The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognized as distinct diseases at this time.

[a] These lesions are classified according to the leukaemia or lymphoma to which they correspond, and are assigned the respective ICD-O code.

itive). For the myeloid neoplasm, further sub-classification is based mainly on their maturation pattern and general biologic features (see below).

The revised classification has some significant departures from the previous edition that can be readily appreciated in Table 1. Among these changes is the recognition that for some lymphoid neoplasms, the age of the patient or the location of the neoplasm may be so closely tied to the biology of the tumor that this information is included in the nomenclature. Examples of age-related neoplasms include pediatric follicular lymphoma, which usually presents with localized disease, a high histologic grade, typically no *BCL2-IGH@* rearrangement, and a good prognosis [9], and EBV positive diffuse large B cell lymphoma of the elderly, which likely arises due to impaired immune surveillance in older individuals (over 50), and are clinically aggressive lymphomas [10]. In addition, the location of some tumors has an impact on the biology of the neoplasm, and is important in denoting it as a specific entity. An example is diffuse large B cell lymphoma of the CNS, which has a distinct gene expression signature [11], and primary cutaneous diffuse large B cell lymphoma, leg-type, which usually has a more aggressive course than other primary cutaneous large B cell lymphomas [12]. Still, it is important to note that although the location of the tumor may relate strongly to the biology of some hematopoietic neoplasms, others disease entities may present as leukemia in the blood or as a tumor in a lymph node or other organ, and the mode of presentation is largely irrelevant to its classification. Examples include chronic lymphocytic leukemia/small lymphocytic lymphoma, acute lymphoblastic leukemia/lymphoblastic lymphoma, and Burkitt lymphoma/leukemia. Despite their different modes of presentation, in each of these examples the neoplastic cells are phenotypically and genotypically identical and thus they are considered as single disease entities. A parallel in the myeloid neoplasms is myeloid sarcoma, an accumulation of myeloblasts in an

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extramedullary location, which should be regarded as synonymous with acute myeloid leukemia or as blast transformation if it occurs in the setting of a myeloproliferative neoplasm or a myelodysplastic syndrome.

The 4th edition of the classification has attempted to more clearly define the minimal diagnostic criteria for some hematopoietic malignancies in which the border between neoplastic and "pre-neoplastic" is not always clear. The frequent application of immunophenotypic and genotypic studies to blood, bone marrow and lymph node samples sometimes uncovers small populations of cells with phenotypic or genetic abnormalities in asymptomatic individuals in whom it is often not clear whether the abnormality is a precursor lesion, is predictive of full-blown disease in the future, or is merely an inconsequential finding. One important example is that of monoclonal B lymphocytosis. Nearly 3% of healthy adults over the age of 40 have clonal populations of B cells with an immunophenotype similar to that of chronic lymphocytic leukemia (CLL), and some of these may have genetic abnormalities identical to those seen in CLL. Only a small fraction of such patients progress to overt CLL, and currently, factors that identify those who will progress are not yet recognized. The minimal diagnostic criterion for CLL has been modified in the revised classification to require $>5 \times 10^9$/L of monoclonal B cells in the peripheral blood, or evidence of extramedullary tissue involvement in cases with lower levels. A level of monoclonal B cells below and without disease elsewhere should be considered as monoclonal B cell lymphocytosis [13].

The 2008 WHO Classification also recognizes that at times some neoplasms exhibit features that overlap different biologic entities, rendering classification difficult if not impossible. Two examples include B-cell lymphoma, unclassifiable, with feature intermediate between diffuse large B cell lymphoma and classical Hodgkin lymphoma, and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma.

Lastly, the proposals for revision and recognition of new entities for the 4th edition were based on studies published in the recent literature. However, to be incorporated into the classification, recent data need to mature and their significance needs to be widely acknowledged. To accommodate more recent information as well as controversial issues, a number of "provisional entities" are included in the classification. These are newly described or characterized disorders that are clinically and/or scientifically important and should be considered for the classification, but for which additional studies are needed to clarify their significance. These appear in Table 1 as italicized entries.

3. Specific comments on the WHO classification of myeloid neoplasms

In the WHO classification, myeloid neoplasms are stratified into those comprised mainly of blasts with minimal if any maturation [acute myeloid leukemia (AML)], and those in which there is maturation, either effective maturation [myeloproliferative neoplasms (MPN)], ineffective maturation with dysplastic features [myelodysplastic syndromes (MDS)] or both ineffective and effective maturation [myelodysplastic/myeloproliferative neoplasms (MDS/MPN)] in the myeloid lineages. The previous (3rd) edition of the WHO classification included, for the first time in any widely used classification, genetic information as criteria not only for the diagnosis of CML, but for some subtypes of AML as well. In the nearly eight years that elapsed between the 3rd and 4th editions of the classification, a number of significant genetic abnormalties were discovered that are associated with subgroups of myeloid neoplasms or with specific disease entities within the subgroups. In some instances, such as in the cases of malignant eosinophilia associated with rearrangements involving *PDGFRA*, *PDGFRB*, or *FGFR1*, the genetic defect, when coupled with the morphology and clinical findings, is the major criterion for naming an entire subgroup of myeloid neoplasms (see Table 1). In other instances, such as the *BCR-ABL1* negative myeloproliferative neoplasms that are often but not invariably associated with the *JAK2* V617F mutation, the genetic defect is an objective criterion of clonality that, when present, identifies the proliferation as neoplastic. Yet, additional criteria are necessary to further define and subtype the diseases associated with the mutated *JAK2*, and to distinguish them from other diseases that share the same mutation. Therefore, although the new classification does incorporate more genetic abnormalities into the myeloid categories as diagnostic criteria, a multiparameter approach is still required. For example, detection of monosomy 5 in a myeloid neoplasm does not identify the lesion as MDS or as AML, rather a carefully performed blast count on the bone marrow samples is required for that distinction.

In some cases, the clinical setting in which the myeloid neoplasm occurs is the primary factor in deciding the classification, trumping even the genetic lesions. This is true for therapy-related MDS and AML (tMDS/tAML). Although it has been argued by some that therapy-related disease shares genetic abnormalities with de novo MDS and AML and could therefore be classified into the subgroups of "AML with recurrent genetic abnormalities," "AML with myelodysplastic related changes" or into the MDS classification, most data indicate that patients with therapy-related disease have a worse prognosis than their de novo counterparts, and that the usual classification schemes correlate poorly with the behavior of therapy-related leukemia [14]. Instead, they are considered as a unique biologic group that should be separately classified and identified, if for no other reason than that patients who have these disorders developed a myeloid neoplasm whereas 95% of the patients treated with similar protocols for the initial disease process do not.

4. Summary

The 4th edition of the WHO classification of hematopoietic and lymphoid neoplasms attempts to provide an up-to-date classification system that is based on recently published peer-reviewed data. Already, in the few months since its publication, new information is accumulating that will eventually lead to our recognition of new entities and that will may require new criteria for old diseases. The WHO effort to keep up-dating the classification will continue on, and hopefully provide a model of cooperation between pathologists, scientists and hematologists from all over the world.

Conflict of interest statement

None declared.

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