

**Society for Hematopathology Scientific Symposium
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**Introduction: The Revised (4th Edition) World Health Organization (WHO)
Classification of Tumors of Hematopoietic and Lymphoid Tissues**

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Bulleted Highlights and Key Words:

- The WHO classification is a collaborative effort of the Society for Hematopathology and the European Association for Haematopathology.
- The WHO classification uses all available information – morphology, cytochemistry, immunophenotype, genetics and clinical features – to define specific disease entities of clinical significance.
- Changes in the revised 4th edition include changes in disease nomenclature, clarification, corrections and/or changes in previous diagnostic criteria, movement of some diseases from one category to another, and addition of new entities and provisional entities
- Provisional entities are recently described disorders for which current data is not yet mature or sufficient to recognize them as full entities, but that merit additional study
- The classification recognizes areas of uncertainty and “gray zones”

Key words: WHO classification, consensus classification, revised classification

Introduction:

The 4th edition of the WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues was a collaborative effort of the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP) sponsored and published by the WHO (1). The aim of the revision process was to incorporate recent relevant scientific and clinical information in order to refine definitions and diagnostic criteria of previously described neoplasms and to introduce newly recognized disease entities. The update began in 2006 when the SH and EAHP selected an 8-member steering committee, composed of representatives of both societies. The steering committee, with the input of both societies, proposed a list of disease entities, chapters and authors. Ultimately over 130 hematologists and pathologists from around the globe were invited to contribute to the monograph, and the IARC appointed the members of the steering committee as editors. In addition, over 60 internationally recognized clinicians and clinical scientists met with the pathology committees in two separate clinical advisory committee (CAC) meetings – one for myeloid neoplasms and one for lymphoid neoplasms – and offered advice that was essential to the revision process as well as providing assurance that the

classification will be clinically useful. Representatives of a number of international consensus groups working on various hematopoietic neoplasms were included in the CAC committees. The final decisions on the classification and disease definitions were reached at a consensus meeting at the IARC headquarters in Lyon, France.

The WHO classification uses all available information – morphology, cytochemistry, immunophenotype, genetics and clinical features – to define clinically significant disease entities, although the relative importance of each of these features varies among the different disorders (2, 3). The revisions made to the previous scheme were based on data published in the literature with the goal of providing an evidence-based classification that can be used in daily clinical practice as well as serving as a basis for future investigation. Although the goal was to “update” the classification, an important consideration was how to incorporate new, often exciting findings that had the potential to change diagnostic criteria or to define newly recognized disease entities, but for which the data was either not yet mature and/or its significance not fully understood. In the case of new entities, the WHO committees approached this issue by designating some as “provisional entities” – disorders for which current evidence is insufficient to recognize them as distinct entities, but which merit additional investigation. Fifteen provisional entities are included in the 4th edition, a considerable jump from the single such disorder found in the preceding monograph. Undoubtedly, as new information accumulates and the classification is reviewed and updated, many of these will be recognized as full entities. Of interest, however, is that the single provisional entity in the 3rd edition, refractory anemia with ring sideroblasts and thrombocytosis (4), is still provisional in the 4th edition, thus illustrating that sometimes as more data is collected, the nature of the disease may remain elusive.

In the revised edition, neoplasms are generally stratified, as in the preceding monograph, according to their lineage of origin (myeloid, B-cell, T-cell and NK-cell, and histiocytic/dendritic cell). Lesions of precursor cells are considered separately from those comprised of more mature cells. Neoplasms of uncertain lineage are usually precursor cell neoplasms that are designated as being of ambiguous lineage, which includes mixed phenotype acute leukemia. However, despite many similarities between the 3rd and 4th editions of the WHO classification, there are significant differences as well. One example illustrative of the evolution of the classification is that some disorders characterized by abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1* – which are almost invariably associated with eosinophilia – may present initially as a myeloid malignancy but culminate as a lymphoid neoplasm, or vice versa (5). These are now recognized as a separate subgroup of neoplasms defined by the genetic rearrangement rather than by their lineage of origin or the maturity of the cells that comprise them. Other changes are too numerous to list here, and will be discussed throughout the symposium, but include new names for old diseases, organizational changes such as movement of entities from one disease category to another, clarification, correction and/or changes in previous diagnostic criteria, and addition of new entities and provisional entities. Furthermore, although the classification attempts to define diseases that are mutually exclusive of each other, it acknowledges that some neoplasms have features that appear to overlap two disease categories and therefore recognizes some “gray zones” such as B-cell lymphomas that have features intermediate

between a diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma or between DLBCL and Burkitt lymphoma (6, 7).

In summary, the multiparameter approach to classification, with an emphasis on defining disease entities, has been proven to be reproducible and clinically useful (3). The goal of the members of the CACs, the authors and editors of the 4th edition of the WHO classification was to provide up-to-date, accurate, and practical criteria for recognition of hematopoietic and lymphoid malignancies. Hopefully, this will facilitate better patient care and the continued discovery of underlying mechanisms of neoplasms that will lead to the development of disease-specific targeted therapy.

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WHO Classification of tumours of haematopoietic and lymphoid tissues

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

MYELOYDYSPLASTIC/ 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*

MYELOYDYSPLASTIC SYNDROMES

Refractory cytopenia with multilineage 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;q22)*; *CBFB-MYH11*

Acute promyelocytic leukaemia
with *t(15;17)(q22;q12)*; *PML-RARA*

AML with *t(9;11)(p22;q23)*; *MLL3-MLL*

AML with *t(6;9)(p23;q34)*; *DEK-NUP214*

AML with *inv(3)(q21q26.2)*
or *t(3;3)(q21;q26.2)*; *RPN1-EV11*

AML (megakaryoblastic)
with *t(1;22)(p13;q13)*; *RBM15-MKLI*

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*

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 hyperdiploidy (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

Extrasosseous 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

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

Lymphocyte-rich 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 tumour

Indeterminate dendritic cell tumour

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)

Classical Hodgkin lymphoma type PTLD

NOS= not otherwise specified.

The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to be fully recognized as distinct diseases at this time; they remain open to further investigation.

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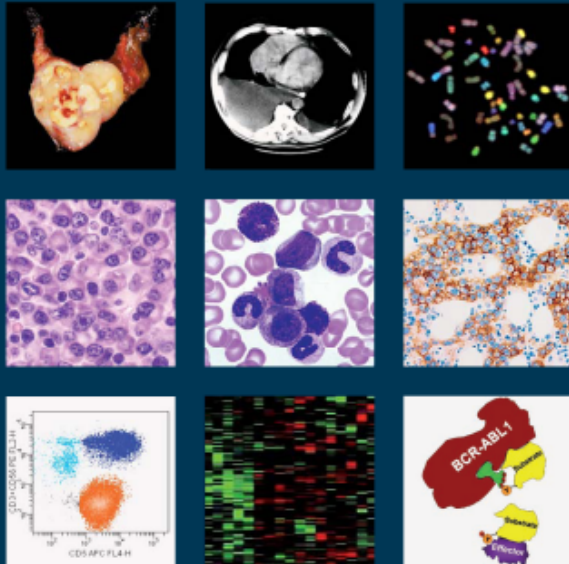
Why classify?

“Classification is the language of medicine: diseases must be described, defined and named before they can be diagnosed, treated and studied. A consensus on definitions and terminology is essential for both clinical practice and investigation.”

N.L. Harris, et al. Introduction to the WHO classification of tumours of haematopoietic and lymphoid tissues, in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman, JW (Eds), IARC, Lyon

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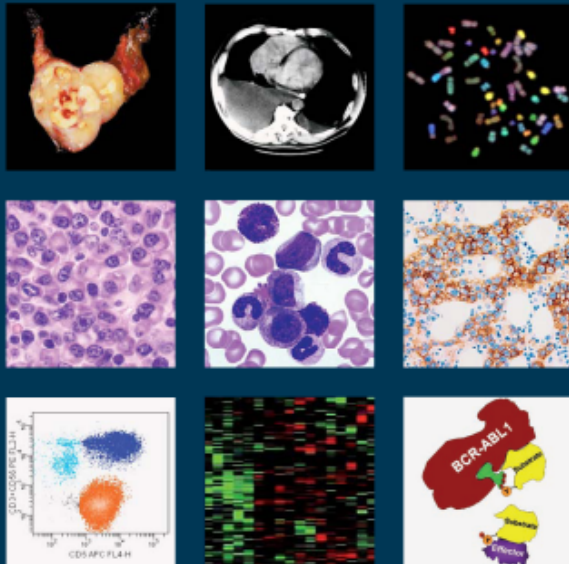
WHO

The 4th Edition of the WHO Classification was a collaborative effort of the EAHP and the SH, sponsored by the WHO.

AIM: To update definitions and diagnostic criteria for diseases described in the 3rd edition and to introduce newly recognized disease entities based on recent information of clinical and scientific relevance.

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman



WHO

Process:

- The EAHP and SH selected an 8-member steering committee comprised of representatives of both societies
- The Steering Committee, with the input of both societies, proposed an updated list of entities and suggested authors to write the chapters
- Ultimately, over 130 hematologists, pathologists and clinical scientists from around the globe participated in the revision process



**The Clinical Advisory Committees
Lymphoid (top) and Myeloid (below)**

Two clinical advisory committees – one for lymphoid and one for myeloid neoplasms – comprised of internationally recognized clinicians/clinical scientists, met with the pathologists to discuss and debate the merits of the proposed classification and revisions





Consensus Conference, Lyon, France, November, 2007

Final consensus decisions on disease entities, definitions and diagnostic criteria were reached during this two-day conference

Principles of the WHO Classification:

- 1) It utilizes all available information – clinical findings, morphology, immunophenotype, and genetic features – in an attempt to define disease entities of clinical significance**
- 2) It is a “consensus” classification in which a majority of experts in various areas have agreed to the definition, criteria for diagnosis and the classification of specific disease entities**
- 3) It is a classification that is amenable to regular updates to allow new information to be incorporated into the scheme**

The 4th Edition of the WHO classification has a number of changes, including:

- New names for old diseases**
- Movement of some diseases from one category to another**
- Clarification, corrections and/or other changes in the definition and in diagnostic criteria for previously described diseases**
- Increasing number of genetic abnormalities as major defining criteria, particularly in the myeloid neoplasms**
- Acknowledgment of areas of uncertainty ("gray zones")**
- Inclusion of a number of "provisional entities" - disorders for which current evidence is insufficient to recognize them as "full" entities but which merit further study**

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An algorithmic approach to the classification of acute leukemia...D. A. Arber

MDS and related disorders ... A. Orazi

Dealing with the histiocytic disorders ... S. A. Pileri

Break

Presentation of Pathologist-in-Training Award ... Dr. L. Peterson

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Applying the new WHO in your diagnostic practice ... N.L. Harris

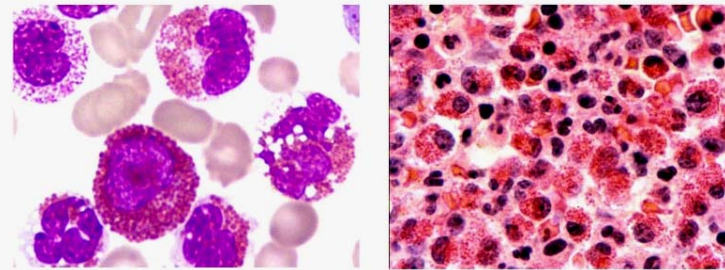
WHO Classification of Myeloid Neoplasms

- I. Myeloproliferative Neoplasms*
- II. Myeloid/Lymphoid Neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1***
- III. Myelodysplastic / Myeloproliferative Neoplasms*
- IV. Myelodysplastic Syndromes
- V. Acute myeloid Leukemia

* Name change

** New category

Myeloid/lymphoid neoplasms with eosinophilia



**Abnormalities of:
PDGFRA, *PDGFRB*,
or *FGFR1***

- Result from abnormal fusion gene encoding an abnormal tyrosine kinase, usually but not invariably with ≥ 1500 eos/uL.
- Rearranged *PDGFRA* usually presents as CEL, often with mast cell proliferation as well; rare cases present as T-LBL with eosinophilia
- Usually rearranged *PDGFRB* has features of CMML with eosinophilia or CEL
- Patients with rearranged *PDGFRA* or *PDGFRB* respond to imatinib
- *FGFR1* rearrangements may present as CEL but presentation as T- or B-LBL/L with eosinophilia is nearly as common, with progression to leukemia with eosinophilia, or vice versa
- Variable clinical and morphologic presentations argued for their placement in a separate and unique subgroup defined largely by the genetic lesion

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