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The 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors

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Abstract: The WHO classification of tumors of various organ systems, also known as the WHO Blue Books, has provided a unified tumor classification system enabling people across the world to share their knowledge and research results. Newer editions with updates have been made every five to ten years to reflect our better understanding of these diseases through the ongoing research work conducted by many researchers and physicians. The last edition of the WHO classification of hematolymphoid tumors was the 4th edition released in 2008 and revised in 2017. Recently, the 5th edition of the WHO classification of hematolymphoid tumors was released, with the online version available since August 2022, and the print version expected to be out at the end of 2022. The 5th edition has been completely rewritten with numerous changes and updates, which include revised hierarchical classification structure, addition or deletion of entities or subtypes, changes or revisions of terminology or nomenclature, revisions or changes of

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diagnostic criteria, and updates of pathogenesis, clinical and genetic features. Stroma-derived tumors of lymphoid tissue and tumor-like lesions have been included for the first time. This chapter provides a brief overview of the 5th edition of the WHO classification of hematolymphoid tumors with a focus on the changes and updates from a reader's perspective.

Keywords: 5th edition of the WHO classification of hematolymphoid tumors; hematolymphoid tumors; hematopoietic neoplasm; lymphoid neoplasm

INTRODUCTION

The World Health Organization (WHO) classification of tumors of various organ systems, also known as the WHO Blue Books, has provided a unified tumor classification system enabling people across the world to share their knowledge and research results. Newer editions with updates have been made every five to ten years to reflect our better understanding of these diseases through the ongoing research work conducted by many researchers and physicians. The last edition of the WHO classification of hematolymphoid tumors was the 4th edition released in 2008 (1), which was revised in 2017 (R4th WHO-Hem) (2). The electronic version of the 5th edition of the WHO classification of hematolymphoid tumors (5th WHO-Hem) was released online in August 2022 (3), and the print version is expected to be out at the end of 2022 (4). The main updates of almost all the entities have been described in two fantastic review articles written by the authors of the 5th WHO-Hem and published in *Leukemia* in July of 2022 (5, 6). With a completely new team of editors and authors, the 5th WHO-Hem has been completely rewritten with significant rearrangement of the contents and numerous changes and updates, which include the addition of some non-hematolymphoid tumors and non-neoplastic lesions for the first time. As a reader, I applaud this great work and appreciate all the authors who have dedicated themselves to this book, and all the researchers whose research findings have contributed significantly to our better understanding of these diseases, although I personally do not think all the changes, especially the change of certain terminologies, are necessary. This chapter provides a brief overview of the 5th WHO-Hem with a focus on the changes and updates from a reader's perspective. Hopefully, it will help other readers in their learning of the 5th WHO-Hem.

REVISED LINEAGE-BASED CLASSIFICATION STRUCTURE AND REARRANGEMENT OF THE CONTENTS

As shown in Figure 1, according to the differentiation of the tumor cells, the majority of hematolymphoid tumors can be classified into one of two general categories: myeloid and lymphoid. The latter is composed of two groups: B-cell and T/NK-cell. Further classification is based on the maturation stage, phenotypic character, histomorphologic features, clinical information, and cytogenetic/molecular genetic findings. To better reflect this lineage-based framework, the 16 chapters of the

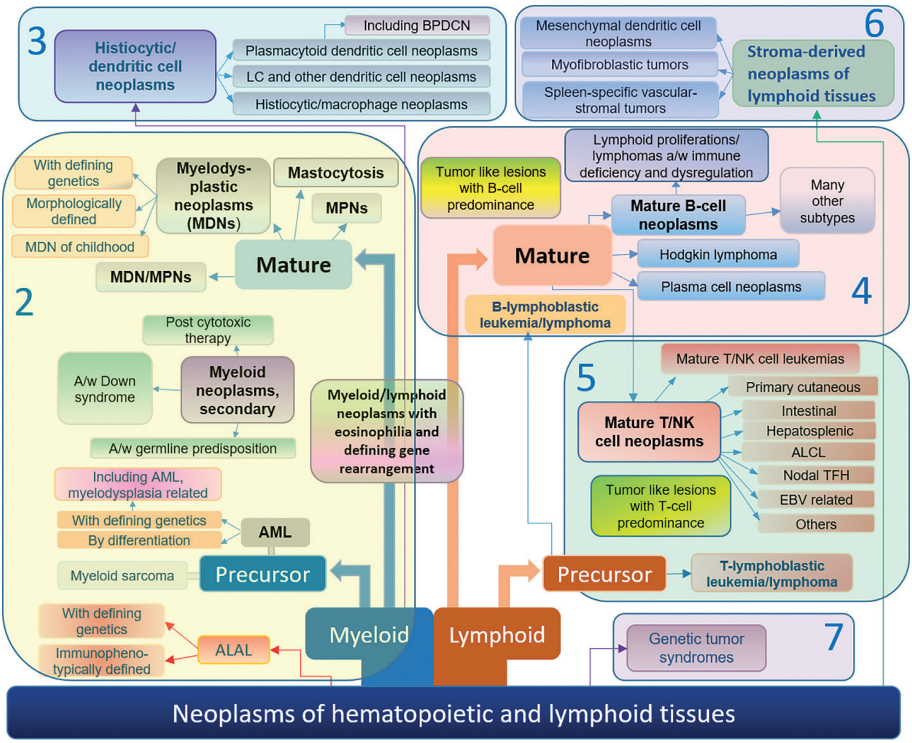

Figure 1. Lineage-based hierarchical classification structure and arrangement of the contents in the 5th edition of WHO classification of hematolymphoid tumors. The numbers represent corresponding chapters: 2, *Myeloid proliferations and neoplasms*; 3, *Histiocytic/Dendritic cell neoplasms*; 4, *B-cell lymphoid proliferations and lymphomas*; 5, *T-cell and NK-cell lymphoid proliferations and lymphomas*; 6, *Stroma-derived neoplasms of lymphoid tissues*; 7, *Genetic tumor syndromes*. ALAL, Acute leukemia of ambiguous lineage; ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; A/w, associated with; BPDCN, blastic plasmacytoid dendritic cell neoplasm; LC, Langerhans cell; MDN, myelodysplastic neoplasm; MPN, myeloproliferative neoplasm; TFH, T follicular helper cell.

R4th WHO-Hem have been combined and rearranged into 4 chapters in the 5th WHO-Hem: *Myeloid proliferations and neoplasms* (chapter 2), *Histiocytic/dendritic neoplasms* (chapter 3), *B-cell lymphoid proliferations and lymphomas* (chapter 4), and *T-cell lymphoid proliferations and lymphomas* (chapter 5). Two new categories, *Stroma-derived neoplasms of lymphoid tissues* (chapter 6) and *Genetic tumor syndromes* (chapter 7), have been added (Figure 1).

To be consistent with other volumes of the 5th edition of WHO Blue Books, each entity in the 5th WHO-Hem has been described under the headings of *Definition*, *ICD-O coding*, *ICD-10 coding* (new), *Related terminology* (replacing *Synonyms* in R4th WHO-Hem), *Subtype(s)*, *Location*, *Clinical features*, *Epidemiology*, *Etiology*, *Pathogenesis* (new), *Macroscopic appearance*, *Histopathology* (replacing *Microscopy*, *Cytochemistry and Immunophenotype* in R4th WHO-Hem), *Cytology* (new), *Diagnostic molecular pathology* (new), *Essential and desirable diagnostic criteria* (new), *Staging*, *Prognosis and prediction*. The *Definition* part is much shorter and

more concise for most of the entities compared with the R4th WHO-Hem. There is a discussion of differential diagnosis at the end of the *Histopathology* section, which is new and overall very useful albeit the variation in length and depth. *Pathogenesis* section describes the evidence or theories of tumorigenesis related to the entity. *Diagnostic molecular pathology* lists the key molecular and/or cytogenetic findings. In the previous editions, well-defined diagnostic criteria had only been given for some myeloid neoplasms and plasma cell neoplasms (1, 2). A big improvement in this edition is the generation of essential diagnostic criteria for all the entities, and desirable diagnostic criteria for some entities.

Myeloid proliferations and neoplasms include 9 sub-categories (families): *Myeloid precursor lesions* (new), *Myeloproliferative neoplasms (MPNs)*, *Mastocytosis*, *Myelodysplastic neoplasms* (*MDNs*, previously known as *myelodysplastic syndrome*, *MDS*), *MDN/MPNs*, *Acute myeloid leukemia (AML)*, *Secondary myeloid neoplasms* (new), *Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement*, *Acute leukemias of mixed or ambiguous lineage*. Juvenile myelomonocytic leukemia (JMML), a subtype of *MDN/MPN* in the R4th WHO-Hem, is now included in the *MPN* family due to its well-established molecular pathogenesis and lack of key features of MDN (7). MDNs in the 5th WHO-Hem are separated into three groups: *MDNs, with defining genetic abnormalities*; *MDNs, morphologically defined*; and *MDNs of childhood*. Blast count (low or increased blasts) has replaced lineage involvement (single or multiple) as a modifier for MDN entities. AML is separated into two groups: *AML with defining genetic abnormalities* and *AML defined by differentiation*. The former contains 13 entities including 2 newly added entities with defining genetic abnormalities and *AML, myelodysplasia related*, which was named "AML with myelodysplasia related changes" and was a separated group in the R4th WHO-Hem (2). *AML defined by differentiation* replaces "AML NOS" in the R4th WHO-Hem (2). Secondary myeloid neoplasms include *Myeloid neoplasm post cytotoxic therapy*, *Myeloid neoplasms associated with germline predisposition,* and *Myeloid proliferations associated with Down syndrome*. AML cases transformed from MPNs are not included in this family, and they should be called MPN in blastic phase. Secondary AML transformed from MDNs or MDN/MPNs belongs to *AML, myelodysplasia related*. Myeloid neoplasms arising in patients with Fanconi anemia, and RASopathies are discussed in the chapter of *Genetic tumor syndromes*. There are three new subtypes (*FLT3* rearrangement, *ETV6::ABL1* fusion, and other tyrosine kinase fusion genes) added into *Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangements*. The entities in *Acute leukemias of mixed or ambiguous lineage* are grouped under either *Acute leukemia of ambiguous lineage (ALAL) with defining cytogenetic abnormalities* or *ALAL, immunophenotypically defined*. The former includes mixed-phenotype acute leukemia (MPAL) with *BCR::ABL1* fusion, MPAL with *KMT2A* rearrangement, and ALAL with other defined genetic alterations. The latter includes ALAL, B/myeloid; ALAL, T/myeloid; ALAL, rare types; ALAL, NOS; and acute undifferentiated leukemia.

B-cell lymphoid proliferations and lymphomas consist of 5 sub-categories (families): *Tumor-like lesions with B-cell predominance* (new), *Precursor B-cell neoplasms*, *Mature B-cell neoplasms*, *Hodgkin lymphoma*, and *Plasma cell neoplasms (PCNs) and other diseases with paraproteins*. Precursor B-cell neoplasms include 12 entities of *B-lymphoblastic leukemia/lymphoma (B-LBL/L) with defined genetic alterations* and *B-LBL/L, NOS*. Mature B-cell neoplasms consist of 12 sub-families/entities: *Pre-neoplastic and neoplastic small lymphocytic proliferations*, *Splenic B-cell*

lymphomas and leukemias, *Lymphoplasmacytic lymphoma*, *Marginal zone lymphoma (MZL)*, *Follicular lymphoma (FL)*, *Cutaneous follicle center lymphoma*, *Mantle cell lymphoma*, *Transformations of indolent B-cell lymphomas* (new), *Large B-cell lymphomas*, *Burkitt lymphoma*, *KSHV/HHV-8 associated B-cell lymphoid proliferations and lymphomas*, *Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation*. The last one replaces *Immunodeficiency-associated lymphoproliferative disorders* (a separated chapter) in the R4th WHO-Hem (2) and includes rare T/NK-cell lymphomas. Large B-cell neoplasms include 18 entities: *Diffuse large B-cell lymphoma, NOS; T-cell/histiocyte-rich large B-cell lymphoma; Diffuse large B-cell lymphoma / high grade B-cell lymphoma with MYC and BCL2 rearrangements*; *ALK-positive large B-cell lymphoma*; *Large B-cell lymphoma with IRF4 rearrangement*; *High grade B-cell lymphoma with 11q aberrations*; *Lymphomatoid granulomatosis*; *EBV-positive diffuse large B-cell lymphoma*; *Diffuse large B-cell lymphoma associated with chronic inflammation*; *Fibrin-associated large B-cell lymphoma*; *Fluid overload-associated large B-cell lymphoma*; *Plasmablastic lymphoma*; *Primary large B-cell lymphoma of immune-privileged sites*; *Primary cutaneous diffuse large B-cell lymphoma, leg type*; *Intravascular large B-cell lymphoma*; *Primary mediastinal large B-cell lymphoma*; *Mediastinal grey zone lymphoma*; and *High-grade B-cell lymphoma, NOS*. Hodgkin lymphomas remain the same, but classic Hodgkin lymphomas are described together with subtypes not separated. The family of *PCNs and other diseases with paraproteins* has been reorganized, and it includes 4 groups: *Monoclonal gammopathies (MGs)*, *Diseases with monoclonal immunoglobulin deposition*, *Heavy chain diseases*, and *PCNs*. MGs consist of *Cold agglutinin disease* (new), *IgM and non-IgM MG of undetermined significance (MGUS)*, *and Gammopathy of renal significance* (*MGRS*, new). PCNs include *Plasmacytoma*, *Plasma cell myeloma/multiple myeloma,* and *PCNs with associated paraneoplastic syndrome*.

T-cell and NK-cell lymphoid proliferations and neoplasms include 3 sub-categories (families): *Tumor-like lesions with T-cell predominance* (new), *Precursor T-cell neoplasms*, and *Mature T-cell and NK-cell neoplasms*. Mature T-cell and NK-cell neoplasms consist of 9 sub-families/entities: *Mature T-cell and NK-cell leukemias* (new), *Primary cutaneous T-cell lymphoid proliferations and lymphomas*, *Intestinal T-cell lymphoid proliferations and lymphomas*, *Hepatosplenic T-cell lymphoma*, *Anaplastic large cell lymphoma*, *Nodal T-follicular helper (TFH) cell lymphoma*, *Other peripheral T-cell lymphomas (peripheral T-cell lymphoma, NOS)*, *EBV-positive NK-cell and T-cell lymphomas*, *EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood*. Mature T-cell and NK-cell leukemias include 6 entities: *T-prolymphocytic leukemia*, *T-large granular lymphocytic leukemia* (*T-LGLL*), *NK-large granular lymphocytic leukemia*, *Adult T-cell leukemia/lymphoma*, *Sezary syndrome*, and *Aggressive NK-cell leukemia*. Primary cutaneous T-cell lymphoid proliferations and lymphomas include 9 entities: *Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder*, *Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder*, *Mycosis fungoides*, *Lymphomatoid papulosis*, *Primary cutaneous anaplastic large cell lymphoma*, *Subcutaneous panniculitis-like T-cell lymphoma*, *Primary cutaneous gamma/delta T-cell lymphoma*, *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma*, and *Primary cutaneous peripheral T-cell lymphoma, NOS*. Intestinal T-cell lymphoid proliferations and lymphomas comprise 5 entities: *Indolent T-cell lymphoma of the gastrointestinal tract*, *Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract*, *Enteropathy-associated T-cell lymphoma*, *Monomorphic epitheliotropic T-cell*

lymphoma, and *Intestinal T-cell lymphoma, NOS*. Nodal TFH cell lymphoma (nTFHcL) has 3 subtypes: *nTFHcL, angioimmunoblastic-type*; *nTFHcL, follicular-type;* and *nTFHcL, NOS*. EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood consist of 4 entities: *Severe mosquito bite allergy*, *Hydro vacciniforme lymphoproliferative disorder*, *Systemic chronic active EBV disease*, and *Systemic EBV-positive T-cell lymphoma of childhood*.

Originated from mesenchymal dendritic cells, *Follicular dendritic cell neoplasms* and *Fibroblastic reticular cell tumor* have been removed from "Histiocytic and dendritic cell neoplasms" to the new category of *Stroma-derived neoplasms of lymphoid tissues*, which also includes *Myofibroblastic tumors* and *Spleen-specific vascular-stroma tumors*. *Genetic tumor syndromes*, another newly added category, includes 4 syndromes: *Fanconi anemia*, *Bloom syndrome*, *Ataxia-telangiectasia syndrome,* and *Rasopathies*.

NEWLY ADDED CATEGORIES, FAMILIES, ENTITIES, AND SUBTYPES

The newly added categories or families are listed in Table 1, and the new entities or subtypes are listed in Table 2 (myeloid) and Table 3 (lymphoid). From these tables, we can see that the 5th WHO-Hem not only identifies or separates many new distinct entities or subtypes, but also expands its territory by including some non-hematolymphoid tumors—stroma-derived neoplasms of lymphoid tissues, as well as some reactive lesions—tumor-like lesions with B-cell or T-cell predominance. Although it is conceptually odd to include these diseases in this WHO Blue Book of hematolymphoid neoplasms, adding them does provide some benefits, such as raising awareness of these lymphoma mimickers and providing convenience for eliminating the need to search for these entities in other books. Besides the follicular dendritic cell neoplasms (categorized in *Histiocytic/dendritic cell neoplasms* in the R4th WHO-Hem), the new category of *Stroma-derived neoplasms of lymphoid tissues* also includes *Intranodal palisaded myofibroblastoma* (a mesenchymal tumor specific to lymph node) and spleen-specific vascular-stromal tumors including *Littoral cell angioma*, *Splenic hamartoma,* and *Sclerosing angiomatoid nodular transformation*. Other stroma-derived tumors located in but not specific to lymph node and spleen are not included here, and they are in the "soft tissue and bone" volume. Tumor-like lesions with B-cell predominance selectively collect 5 entities: *Reactive B-cell rich lymphoid proliferations that mimic lymphoma (RBRLPs)*, *IgG4-related disease* and 3 types of *Castleman disease*. RBRLPs include florid follicular hyperplasia, progressive transformation of germinal center, EBV-associated lymphadenopathy, autoimmune associated lymphadenopathy, indolent B-lymphoblastic proliferation, etc. Although these lesions are commonly encountered or considered during lymphoma workup, actually all the benign lymphadenopathies and other related lesions mimic lymphomas in some way, and their possibilities should always be explored before the final diagnosis. The histological finding of lymph nodes involved by IgG4-related disease is often variable, which makes the diagnosis very challenging and leads to a broad differential diagnosis including some lymphomas (8). Unicentric Castleman disease, idiopathic multicentric Castleman disease and KSHV/HHV8 associated Castleman disease share

TABLE 1 **Newly added categories or families in the 5th edition of WHO classification of hematolymphoid tumors**

Under the category of	Newly added category/family
Chapters	Stroma-derived neoplasms of lymphoid tissues Genetic tumor syndromes
Myeloid neoplasms	Myeloid precursor lesions Secondary myeloid neoplasms
Histiocytic/dendritic cell neoplasms	Plasmacytoid dendritic cell neoplasms
B-cell lymphoid proliferations and neoplasms	Tumor-like lesions with B-cell predominance
Mature B-cell neoplasms	Large B-cell lymphomas
T/NK-cell lymphoid proliferations and neoplasms	Tumor-like lesions with T-cell predominance
Mature T/NK cell neoplasms	Mature T-cell and NK-cell leukemias Primary cutaneous T-cell lymphoproliferations and lymphomas Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas EBV-positive T/NK-cell lymphomas Nodal T-follicular helper (TFH) cell lymphoma
Stroma-derived neoplasms of lymphoid tissues	Mesenchymal dendritic cell neoplasms Myofibroblastic tumors Spleen-specific vascular-stromal tumors

some histologic features, but they have different etiology, pathogenesis, and clinical course, and should be diagnosed distinctively in conjunction with clinical features and the results of the other tests. Tumor-like lesions with T-cell predominance include *Kikuchi-Fujimoto disease*, *Autoimmune lymphoproliferative syndrome (ALPS)*, and *Indolent T-lymphoblastic proliferation (ITLP)*. ITLP shows proliferation of non-clonal T-lymphoblasts in the lymph node with preserved nodal architecture. ITLP can be associated with benign lesions such as Castleman disease or certain malignancies (9). Rare T-lymphoblastic lymphoma cases may have features of ITLP (10); therefore, a comprehensive workup is always required to rule out T-lymphoblasts lymphoma for all ITLP cases. Besides the characteristic coagulative necrosis, Kikuchi-Fujimoto disease can have frequent large immunoblasts and histiocytes, which can mimic high grade lymphomas or histiocytic sarcoma. ALPS usually shows interfollicular proliferation of CD4/CD8 dual negative T cells and a high proliferation index, which can mimic T-cell lymphomas.

In line with other WHO series, the 5thWHO-Hem has also generated a category of *Genetic tumor syndromes* to include genetic syndromes associated with increased risk for hematolymphoid tumors. These genetic syndromes include *Fanconi anemia*, *Ataxia telangiectasia*, *Bloom syndrome,* and *RASopathies*. Some genetic diseases with increased risk for myeloid malignancies, such as *GATA2*-deficiency, Shwachman-Diamond syndrome, dyskeratosis congenita, etc., are not included here. Instead, they are described in *Myeloid neoplasms associated with germline predisposition* in the family of *Secondary myeloid neoplasms*. Myeloid neoplasms with germline

TABLE 2 **Newly added or deleted entities/subtypes in myeloid and mesenchymal neoplasms in the 5th edition of WHO classification of hematolymphoid tumors**

Under the category/family/entity of	Newly added entity/subtype
Myeloid precursor lesions	Clonal hematopoiesis Clonal cytopenia of undetermined significance
Systemic mastocytosis	Bone marrow mastocytosis
MDN with defining genetic abnormalities	MDN with low blasts and *SF3B1* mutation MDN with biallelic *TP53* inactivation
MDN, morphologically defined	MDN with low blasts MDN, hypoplastic
AML with defining genetic abnormalities	AML with *NUP98* rearrangement AML with other defined genetic alterations
AML with other defined genetic alterations	AML with *RUNX1T3*(*CBFA2T3*)*::GLIS2* AML with *KAT6A::CREBBP* AML with *FUS::ERG* AML with *MNX1::ETV6* AML with *NPM1::MLF*
ALAL with defining genetic abnormalities	ALAL with other defined genetic alterations
ALAL with other defined genetic alterations	MPAL with *ZNF384* rearrangement ALAL with *BCL11B* rearrangement
Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement	Myeloid/lymphoid neoplasm with *FLT3* rearrangement Myeloid/lymphoid neoplasm with *ETV6::ABL1* fusion Myeloid/lymphoid neoplasms with other tyrosine kinase fusion genes
Plasmacytoid dendritic cell neoplasms	Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Histiocyte/macrophage neoplasms	Rosai-Dorfman disease ALK-positive histiocytosis
Myofibroblastic tumors	Intranodal palisaded myofibroblastoma
Spleen-specific vascular-stromal tumors	Littoral cell angioma Splenic hamartoma Sclerosing angiomatoid nodular transformation of spleen
	Deleted entity/subtype
Myeloproliferative neoplasms	Accelerated phase of CML
MDS	MDS with single lineage dysplasia MDS with multilineage dysplasia MDS, unclassifiable
AML	AML with mutated RUNX1 Acute panmyelosis with myelofibrosis

ALAL, acute leukemia of ambiguous lineage; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDN, myelodysplastic neoplasm; MDS, myelodysplastic syndrome; MPAL, mixed-phenotype acute leukemia.

TABLE 3 Newly added or deleted entities/subtypes in lymphoid neoplasms in the 5th edition of WHO classification of hematolymphoid tumors

Under the category/family/entity of	Newly added entity/subtype
TL-lesions with B-cell predominance	Reactive B-cell rich lymphoid proliferations that can mimic lymphoma IgG4 related disease Unicentric Castleman disease Idiopathic multicentric Castleman disease KSHV/HHV8-associated multicentric Castleman disease
B-lymphoblastic leukemias/lymphomas (B-LBL/L)	B-LBL/L with *ETV6::RUNX1*-like features B-LBL/L with *TCF3::HLF* fusion B-LBL/L with other defined genetic alterations
Mature B-cell neoplasms	Transformations of indolent B-cell lymphomas
Splenic B-cell lymphomas and leukemias	Splenic B-cell lymphoma/leukemia with prominent nucleoli
Marginal zone lymphoma	Primary cutaneous marginal zone lymphoma
Large B-cell lymphomas	Fluid overload-associated large B-cell lymphoma Primary large B-cell lymphoma of immune-privileged sites
Primary large B-cell lymphoma of immune-privileged sites	Primary large B-cell lymphoma of the vitreoretina Primary large B-cell lymphoma of the testis
LPs and lymphomas associated with ID and dysregulation	Hyperplasias arising in ID/dysregulation Polymorphic lymphoproliferative disorders arising in ID/dysregulation Lymphomas arising in ID/ dysregulation
Follicular lymphoma	Classic follicular lymphoma Follicular large B-cell lymphoma Follicular lymphoma with uncommon features
Monoclonal gammopathies	Cold agglutinin disease Monoclonal gammopathy of renal significance
PCNs with associated paraneoplastic syndrome	AESOP syndrome
TL-lesions with T-cell predominance	Kikuchi-Fujimoto disease Autoimmune lymphoproliferative syndrome Indolent T-lymphoblastic proliferation
Primary cutaneous T-cell lymphoproliferations and lymphomas	Primary cutaneous peripheral T-cell lymphoma, NOS
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas	Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
EBV-positive NK/T-cell lymphomas	EBV-positive nodal T- and NK-cell lymphoma
	Deleted entity/subtype
Precursor lymphoid neoplasms	NK-lymphoblastic leukemia / lymphoma
Mature B-cell neoplasms	B-cell prolymphocytic leukemia

ID, immune deficiency; LP, lymphoid proliferation; NOS, not otherwise specified; PCN, plasma cell neoplasm; TL, tumor-like.

predisposition and potential organ dysfunction include two new genetic diseases: germline *SAMD9* mutations (*MIRAGE syndrome*) and Germline *SAMD9L* mutations (*SAMD9L-related Ataxia Pancytopenia syndrome*). Germline *TP53* mutation (*Li-Fraumeni syndrome*) has been added to *Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction*.

Myeloid precursor lesions have been included as a family for the first time in this book under the category of *Myeloid proliferations and neoplasms*. Clonal hematopoiesis (CH) refers to the presence of a population of blood and/or bone marrow cells that share an acquired mutation or chromosome abnormality. The incidence of CH increases with age (11), which is reflected in the term—*Aging-related CH (ARCH)*. There are no well-defined criteria for CH and ARCH. In contrast, *Clonal hematopoiesis of indeterminate potential (CHIP)* is a well-defined term, and it refers to the CH carrying somatic mutations of myeloid malignancy-associated genes with a variant allele fraction (VAF) ≥ 2% (≥4% for X-linked gene mutations in males) and without unexplained cytopenia or a diagnosis of hematologic disease (12). CHIP has an increased risk for myeloid malignancy with a progression rate of 0.5–1% /year, and it also has an increased risk of cardiovascular disease and overall mortality (13). *Clonal cytopenia of undetermined significance (CCUS)* refers to the presence of persistent (> 4 months) cytopenia(s) in the patient meeting the other diagnostic criteria of CHIP. CCUS has an increased risk for myeloid malignancy, which varies according to clone size, number of somatic mutations and the presence of certain gene mutations.

Plasmacytoid dendritic cell neoplasms are a new family in the category of *Histiocytic/dendritic cell neoplasm*. They include *Blastic plasmacytoid dendritic cell neoplasm* and *Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm*. The former was described in a separate chapter in the R4th WHO-Hem (2). The latter is a new entity that refers to a clonal proliferation of plasmacytoid cells with low grade morphology and in association with chronic myelomonocytic leukemia (CMML), AML, MDN or MPN. There are two entities, *Rosai-Dorfman disease (RDD)* and *ALK-positive histiocytosis*, newly added to *Histiocyte/macrophage neoplasms*. The presence of frequent gain-of-function gene mutations in MAPK signaling pathway in RDD indicates that it is a neoplastic disease (14). ALK-positive histiocytosis is characterized by the presence of *ALK* gene translocation (most commonly *KIF5B::ALK*), and it responds to ALK-inhibitor therapy, although it has a broad clinicopathological spectrum (15, 16). The infant form usually involves hematolymphoid tissues and other systems, showing systemic symptoms, and often remitting spontaneously or after chemotherapy. ALK-positive histiocytosis can also occur in other age groups with involvement of multiple organ systems or one organ system. The histomorphology of *ALK-positive histiocytosis* overlaps with that of *Juvenile xanthogranuloma (JXG)*. Therefore, histiocytic proliferations, especially those with the morphology of JXG, should be stained for ALK to rule out ALK-positive histiocytosis.

As shown in Table 2 and Table 3, there are new genetic abnormalities identified as distinct subtypes in AML, ALAL, B-LBL/L, MDN, and myeloid and lymphoid neoplasms with eosinophilia. These new subtypes include *SF3B1* mutation and *TP53* inactivation in MDN, *NUP98* rearrangement in AML, *ZNF384* rearrangement and *BCL11B* rearrangement in ALAL, *TCF3::HLF* fusion, *ETV6::RUNX1*-like features in B-LBL/L, *FLT3* rearrangements, *ETV6::ABL1* fusion, and novel types of *JAK2* rearrangements in *myeloid/lymphoid neoplasms with eosinophilia*

and defining gene rearrangement. A new subtype named "*XXX* (*entity name) with other defined genetic alterations*" is added to all these entities to accommodate the provisional subtypes with distinct genetic features.

As shown in Table 3, there are quite a lot of new entities or subtypes added to *Mature B-cell neoplasms*. Splenic B-cell lymphoma/ leukemia with prominent nucleoli is a new entity that includes the cases of *Hairy cell leukemia variant* and *CD5-negative B-cell prolymphocytic leukemia* of the R4th WHO-Hem (2). Two new subtypes of FL, *Follicular large B-cell lymphoma (FLBL)* and *FL with uncommon features (uFL)* have been recognized besides the *Classic FL (cFL)* that represents the majority (85%) of FL cases, with *BCL2* rearrangement and at least in part a follicular growth pattern. The FLBL subtype mostly represents FL grade 3B in the R4th WHO-Hem, and the uFL subtype includes two subsets with histomorphologic features significantly different from cFL. One subset shows blastoid or large centrocyte cytology, and the other demonstrates a predominantly diffuse growth pattern. The former more frequently shows variant immunophenotypic and genotypic features and is likely associated with an inferior survival outcome (17). *Large B-cell lymphomas (LBCLs)* is a newly added family in the 5th WHO-Hem, which consists of 17 distinct entities except for DLBCL, NOS. *LBCL of immune-privileged sites* is a new entity describing a group of aggressive B-cell lymphomas that share common biological features and arise as primary lymphomas in the central nervous system, the vitreoretinal compartment, or the testes. *Fluid overload-associated LBCL* is also a new entity that is frequently associated with an underlying condition causing fluid overload (18). It is distinct from primary effusion lymphoma by its different immunophenotype and lack of association with KSHV/HHV8. *Transformation of indolent B-cell lymphomas* is a new group of mature B-cell neoplasms including aggressive lymphomas arising in patients with a clonally related indolent B-cell lymphoma. The format for reporting transformed lymphomas is: aggressive lymphoma entity, followed by "transformed from" and the name of the related indolent lymphoma. Monoclonal gammopathy of renal significance (MGRS), cold agglutinin disease, and AESOP syndrome (adenopathy and extensive skin patch overlying a plasmacytoma) have been added to *PCNs and other diseases with paraproteins* in the 5th WHO-Hem. Cold agglutinin disease is autoimmune hemolytic anemia caused by monoclonal cold agglutinins originating from a clonal B-cell proliferation not meeting the criteria for a B-cell lymphoma (19). MGRS refers to a plasma cell or B-cell proliferation not fulfilling the criteria for lymphoma but secreting a monoclonal immunoglobulin resulting in kidney injury (20).

There are 3 new entities added to the family of *Mature T-cell and NK-cell neoplasms*. *Primary cutaneous peripheral T-cell lymphoma, NOS*, represents the primary cutaneous T-cell lymphomas (CTCLs) that don't meet the diagnostic criteria of the established CTCL entities. *Indolent NK-cell lymphoproliferative disorder of the GI tract*, previously known as a reactive process, is included as a new entity in the category of *Intestinal T/NK-cell proliferations and neoplasms*. It has somatic mutations related to JAK-STAT signaling pathway and is negative for EBV infection. *Nodal EBV-positive T and NK-cell lymphoma* is added as a new entity in the group of *EBV-positive NK/T cell lymphomas* besides the relatively common *Extranodal NK/T-cell lymphoma*. EBV-positive nodal T and NK-cell lymphoma occurs mostly in East Asians with poor prognosis and distinct genetic features (21).

DELETED ENTITIES/SUBTYPES

Compared with the many new entities and terminology changes, the number of entities or subtypes completely removed is very limited (see Table 2 and Table 3). With the clinical application of tyrosine kinase inhibitors (TKIs) and careful disease monitoring in chronic myeloid leukemia (CML), the progression to advanced phase disease is uncommon, and the designation of an accelerated phase (AP) is not very relevant to disease deterioration. Therefore, the AP of CML is removed in the 5th WHO-Hem in order to emphasize other risk features related to TKI resistance. With the significantly different nomenclature, the MDN entities based on single- /multilineage dysplasia or ring sideroblasts do not exist anymore. In addition, *MDS, unclassifiable*, as seen in the R4th WHO-Hem, is deleted. *AML with RUNX1 mutations* is removed because of its lack of enough specificity. *B-cell prolymphocytic leukemia* is deleted due to its heterogeneous nature, and the cases now belong to *Splenic B-cell lymphoma/leukemia with prominent nucleoli* (new), *Transformations of indolent B-cell lymphomas* (new), or *Mantle cell lymphoma,* respectively. NK-lymphoblastic leukemia/lymphoma, a provisional entity in the R4th WHO, is not listed in the 5th WHO-Hem due to the lack of clear-cut and reliable diagnostic criteria.

REVISED NOMENCLATURE AND TERMINOLOGY CHANGES

As we can see from Table 4 and Table 5, there are many terminology changes or nomenclature revisions. Most of the changes are to reflect our better understanding of these diseases. In contrast, one type of name change is to harmonize the nomenclature with other fields and the rest of the WHO 5th edition series. For example, the Human Genome Organization Gene Nomenclature Committee has recommended the new designation of gene fusions using double colon marks (::) (22). Hence, double colon marks replace the hyphen to join two fusion gene partners as used in previous editions (1, 2). This format change of gene fusion in myeloid neoplasms is not listed in Table 4. The International Union of Immunological Societies has renamed *primary immunodeficiencies associated with germline mutations* as “inborn errors of immunity”, and the 5th WHO-Hem has adopted this terminology. Another type of name change is purely language editing, e.g., “excess blasts” to “increased blasts”, “classical” to “classic”. Fortunately, there is only a very limited number of this type of name change. We can optimistically call this type of change as “job security type”. The qualifier “unclassifiable” used for some entities in the R4th WHO-Hem (2) sounds paradoxical, and it has been replaced with “NOS” or the whole entity has been removed in the 5th WHO-Hem.

The 5thWHO-Hem uses *Myelodysplastic neoplasm (MDN)* to replace *Myelodysplastic syndrome (MDS)* with the purpose to emphasize their neoplastic nature and being terminologically consistent with *MPN*. MDNs have been reclassified based primarily on the presence of recurrent cytogenetic abnormalities and blast count. Single/multiple lineage dysplasia and ring sideroblasts are not used to classify MDN anymore. Childhood MDNs have different biological

TABLE 4 Revised nomenclature and name changes of myeloid or mesenchymal neoplasms in the 5th edition compared with the revised 4th edition of WHO classification of hematolymphoid tumors

WHO classification, 5th edition	WHO classification, revised 4th edition
Myeloid proliferations and neoplasms	
Chronic myeloid leukemia	Chronic myeloid leukemia, *BCR-ABL1*–positive
Chronic eosinophilic leukemia	Chronic eosinophilic leukemia, not otherwise specified
Myeloproliferative neoplasm, not otherwise specified	Myeloproliferative neoplasm, unclassifiable
Myelodysplastic neoplasms (MDNs) MDN, with defining genetic abnormalities MDN with low blasts and 5q deletion MDN with low blasts and *SF3B1* mutation MDN with biallelic *TP53* inactivation MDN, morphologically defined MDN with low blasts MDN, hypoplastic MDN with increased blasts MDNs of childhood Childhood MDN with low blasts Childhood MDN with increased blasts	Myelodysplastic syndromes (MDSs) MDS with single lineage dysplasia MDS with ring sideroblasts MDS with multilineage dysplasia MDS with excess blasts MDS with excess blasts and erythroid predominance MDS with excess blasts and fibrosis MDS with isolated del(5q) MDS, unclassifiable Childhood MDS Refractory cytopenia of childhood
Myelodysplastic/myeloproliferative neoplasm with neutrophilia	Atypical chronic myeloid leukemia, *BCR-ABL1*–negative
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis	Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, NOS	Myelodysplastic/myeloproliferative neoplasm, unclassifiable
AML with defining genetic abnormalities	AML with recurrent genetic abnormalities
AML with *KMT2A* rearrangement	AML with t(9;11)(p21.3;q23.3); *KMT2A-MLLT3*
AML with *MECOM* rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML with *CEBPA* mutation	AML with biallelic mutation of *CEBPA*
Acute erythroid leukemia	Pure erythroid leukemia
AML, myelodysplasia-related	AML with myelodysplasia-related changes
Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement	Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement
Myeloid/lymphoid neoplasm with *JAK2* rearrangement	Myeloid/lymphoid neoplasms with *PCM1-JAK2*
Stroma-derived neoplasms of lymphoid tissues	
EBV-positive inflammatory follicular dendritic cell sarcoma	Inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma

AML, acute myeloid leukemia.

TABLE 5 **Revised nomenclature and name changes of lymphoid neoplasms in the 5th edition compared with the revised 4th edition of WHO classification of hematolymphoid tumors**

WHO classification, 5th edition	WHO classification, revised 4th edition
B-CELL lymphoid proliferations and lymphomas	
B-LBL/L with **high** hyperdiploidy	B-LBL/L with hyperdiploidy
B-LBL/L with *BCR::ABL1* fusion	B-LBL/L with t(9;22)(q34;q11.2); *BCR-ABL1*
B-LBL/L with *BCR::ABL1*-like features	B-LBL/L, *BCR-ABL1*-like
B-LBL/L with *KMT2A* rearrangement	B-LBL/L with t(v;11q23.3); *KMT2A*-rearranged
B-LBL/L with *ETV6:: RUNX1* fusion	B-LBL/L with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-LBL/L with *TCF3::PBX1* fusion	B-LBL/L with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-LBL/L with *IGH::IL3* fusion	B-LBL/L with t(5;14)(q31.1;q32.1); *IGH/IL3*
In situ follicular B-cell **neoplasm**	In situ follicular **neoplasia**
In situ mantle cell **neoplasm**	In situ mantle cell **neoplasia**
DLBCL/ HGBCL with *MYC* and *BCL2* rearrangements	HGBCL with *MYC* and *BCL2* **and/or *BCL6*** rearrangements
High-grade B-cell lymphoma with 11q aberrations	**Burkitt-like** lymphoma with 11q aberration
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, **NOS**
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL
KSHV/HHV8-positive DLBCL	HHV8-positive DLBCL, **NOS**
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation	Immunodeficiency-associated lymphoproliferative disorders
Inborn error of immunity-associated lymphoid proliferations and lymphomas	Lymphoproliferative diseases associated with **primary immune disorders**
Plasma cell neoplasms and other diseases with paraproteins (family name)	Plasma cell neoplasms (family name)
Immunoglobulin-related (AL) amyloidosis	Primary amyloidosis
Monoclonal immunoglobulin deposition disease	Light chain and heavy chain deposition disease
T-/ NK-cell lymphoid proliferations and lymphomas	
T-LBL/L, **NOS**	T-LBL/L
Early T-precursor lymphoblastic leukemia / **lymphoma**	Early T-cell precursor lymphoblastic leukemia
T-large granular lymphocytic leukemia	T-cell large granular lymphocytic leukemia

(Continued)

TABLE 5 **Revised nomenclature and name changes of lymphoid neoplasms in the 5th edition compared with the revised 4th edition of WHO classification of hematolymphoid tumors (*Continued*)**

WHO classification, 5th edition	WHO classification, revised 4th edition
NK-large granular lymphocytic leukemia	Chronic lymphoproliferative disorder of NK cells
Primary cutaneous acral CD8-positive **lymphoproliferative disorder**	Primary cutaneous acral CD8-positive T-cell **lymphoma**
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas (family name)	Intestinal T-cell lymphoma (family name)
Indolent T-cell **lymphoma** of the gastrointestinal tract	Indolent T-cell **lymphoproliferative disorder** of the gastrointestinal tract
Nodal TFH cell lymphoma, angioimmunoblastic-type	Angioimmunoblastic T-cell lymphoma
Nodal TFH cell lymphoma, follicular-type	Follicular T-cell lymphoma
Nodal TFH cell lymphoma, NOS	Nodal peripheral T-cell lymphoma with TFH phenotype
Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma, **nasal-type**
Hydroa vacciniforme lymphoproliferative disorder	Hydroa vacciniforme-**like** lymphoproliferative disorder
Systemic chronic active EBV disease	Chronic active EBV infection of T- and NK-cell type, systemic form

CHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma; LBL/L, lymphoblastic leukemia/lymphoma.

and genetic features from adult MDNs. *Childhood MDN with low blasts* replaces the term "Refractory cytopenia of childhood" used in the R4th WHO-Hem (2). It includes two subtypes: *Childhood MDN with low blasts, hypocellular*; and *Childhood MDN with low blasts, NOS*. *Childhood MDN with increased blasts* refers to the cases with ≥2% blasts in the peripheral blood and/or ≥5% blasts in the bone marrow.

Because of the presence of multiple translocation partner genes in the entities with a key gene involvement, only the key genes are listed in the names of these entities, e.g., AML with *KMT2A* rearrangement. Since the typical translocation or inversion may not be demonstrated by conventional cytogenetic study, the chromosomal changes are removed from the names of these entities (not listed in Table 4), e.g., AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* changed to AML with *RUNX1::RUNX1T1*. Similar changes are also made for the entities with defining genetic abnormalities of B-LBL/L and myeloid/lymphoid neoplasms with eosinophilia. The revised name of *AML with biallelic mutation of CEBPA* in the R4th WHO-Hem (1, 2) has been changed back to the name without "biallelic" to include single mutations located in the basic leucine zipper region of the gene, which also showed the association with favorable prognosis (23). *AML with myelodysplasia-related changes* is now renamed as "AML, myelodysplasia-related

(AML-MR)". *Pure erythroid leukemia* is renamed as "Acute erythroid leukemia" with the purpose to keep the name more consistent with other subtypes.

There are lots of name changes or nomenclature revisions in mature B-cell neoplasms. The addition of *BCL2* rearrangement besides *MYC* rearrangement is the only requirement for the revised entity *DLBCL/HGBL with MYC and BCL2 rearrangements*. The *BCL6* rearrangement is removed from this entity because the lymphomas with dual *MYC* and *BCL6* rearrangements are more diverse and show gene expression profile and mutational landscape significantly different from lymphomas with dual *MYC/BCL2* rearrangements (24). Those cases with *MYC* and *BCL6* dual rearrangements are now classified as either a subtype of *DLBCL, NOS* or *HGBL, NOS* depending on their cytomorphologic features. *Burkitt-like lymphoma with 11q aberration* in the R4th WHO-Hem is now named as *High-grade B-cell lymphoma with 11q aberration*. *Mediastinal gray zone lymphoma* replaces the old term *B-cell-lymphoma, unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma*. The group of immunodeficiency-associated lymphoproliferative disorders has been renamed as " *Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation*" and included in the family of *Mature B-cell neoplasms* in the 5th WHO-Hem. The reorganization of the lymphoid proliferations and lymphomas in this group reflects the consensus gained from the *Workshop on Immunodeficiency and Dysregulation* organized by the Society of Hematopathology and European Association for Hematopathology in 2015 (25, 26). The new framework recognizes the same histopathologic features shared by the diseases with different underlying causes of immunodeficiency. Three-part nomenclature is recommended for the diagnosis of the disorders in this group, and it includes histological diagnosis, viral association, and immune deficiency/dysregulation setting. Histological subtypes include hyperplasia (specify type), polymorphic lymphoproliferative disorder, mucocutaneous ulcer, and lymphoma (same diagnostic criteria as for immunocompetent patients). The associated viruses are mostly EBV and KSHV/HHV8. Immune deficiency/dysregulation settings include inborn error of immunity (specify type), HIV infection, posttransplant (solid organ or bone marrow), autoimmune disease, iatrogenic/therapy-related (specify) and immune senescence.

There are also quite a few nomenclature revisions and name changes in mature T/NK cell neoplasms. *NK-large granular lymphocytic leukemia* replaces "Chronic lymphoproliferative disorder of NK cells" given recent evidence that it is monoclonal and shares many similarities with T-LGLL. *Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract* in the R4th WHO-Hem has been renamed as "indolent T-cell lymphoma of the gastrointestinal tract" to highlight its clinical features of persistence and poor response to chemotherapy. *nTFHcL angioimmunoblastic-type*, *nFTHcL follicular type* and *nTFHcL NOS* have replaced the previous subtype names "Angioimmunoblastic T-cell lymphoma", "Follicular T-cell lymphoma" and "Peripheral T cell lymphoma with TFH phenotype", respectively. The changes are to recognize their similarities in clinical presentation, immunophenotype and genetic features (27). The qualifier "nasal-type" of *Extranodal NK/T-cell lymphoma* has been removed in the 5th WHO-Hem in order to recognize the presence of this disease at various extranodal sites. *Chronic active EBV infection, systemic form* has been renamed as "Systemic chronic active EBV disease" to emphasize its overall fatal outcome.

REVISED DIAGNOSTIC CRITERIA

In the R4th WHO-Hem and other previous editions, well-defined diagnostic criteria are only provided for some myeloid neoplasms and plasma cell neoplasms. As a big improvement, all the entities in WHO Blue Books of the 5th edition have essential diagnostic criteria, and some entities also have desirable diagnostic criteria. Essential diagnostic criteria list the diagnostic elements required to make the diagnosis, while desirable diagnostic criteria list the finding(s) supporting the diagnosis, but not mandatory. Although the diagnosis is always the best judgment of a pathologist based on all the information he/she has, these diagnostic criteria do assist in the workup of the cases and making the diagnosis, especially for the junior pathologists or young attendings. Of course, not all diagnostic criteria are perfectly formulated, and more refinements or revisions are expected to see in future editions.

There are quite a lot of changes made to the existing diagnostic criteria. Besides the previously defined two criteria (≥20% myeloid blasts and extramedullary proliferation of blasts), the blast phase of CML has one more criterion in the 5th WHO-Hem: presence of bona fide lymphoblasts in the peripheral blood or bone marrow (even if <10%). The diagnostic criteria of chronic eosinophil leukemia (CEL) have been revised, and the changes include: (i) the time interval required to define sustained hypereosinophilia decreased from 6 months to 4 weeks; (ii) requirement of both clonality and abnormal bone marrow morphology; (iii) removal of increased blasts (≥2% in peripheral blood or 5–19% in bone marrow) as an alternative to clonality. The revised criteria lead to a better distinction between CEL and other diseases with hypereosinophilia (28). JMML is now a subtype of MPN, and it also has revised diagnostic criteria. The changes to the diagnostic criteria of JMML include: (i) absence of *KMT2A* rearrangements as one of the required diagnostic criteria; (ii) elimination of monosomy 7 as a cytogenetic criterion; (iii) hypersensitivity to GM-CSF by colony assay and STAT5 hyperphosphorylation combined as one minor criterion; (iv) thrombocytopenia with hypercellular bone marrow added as one minor criterion. Diagnostic criteria of chronic myelomonocytic leukemia (CMML) have been revised and they consist of prerequisite and supporting criteria. The cutoff for absolute monocytosis (the first prerequisite criterion) is lowered from $\geq 1.0 \times 10^9$ /L to $\geq 0.5 \times 10^9$ /L. Other prerequisite criteria include <20% blasts, not meeting the diagnostic criteria for MPNs and myeloid/lymphoid neoplasms with eosinophilia. Supporting criteria include dysplasia, clonality, and abnormally increased fraction of classical monocytes (newly added criterion) (29). If monocytosis is $\geq 1.0 \times 10^9$ /L, prerequisite criteria plus one of the supporting criteria can make the diagnosis. If monocytosis is $< 1.0 \times 10^9$ /L, detection of clonal cytogenetic or molecular abnormality and documentation of dysplasia are required for the diagnosis. Two new subtypes of CMML are introduced based on white blood cell count (WBC): myelodysplastic CMML (WBC $< 13 \times 10^9$ /L) and myeloproliferative CMML (WBC $\geq 13 \times 10^9$ /L).

The cut-off of blast percentage to define AML is arbitrary, and the blast enumeration can vary due to sampling variations and subjective evaluation. In the 5th WHO-Hem, the cutoff value of 20% blasts is not required for the diagnosis of AML if the leukemic blasts harbor *PML::RARA, RUNX1-RUNX1T1, CBFB-MYH11,*

DEK::NUP214, RBM15::MRTFA, KMT2A rearrangement, *MECOM* rearrangement, *NUP98* rearrangement, or *NPM1* mutation; while in the R4th WHO-Hem, only the first three genetic abnormalities listed here had this privilege. The diagnostic criteria for AML-MR have also been revised. Multilineage dysplasia has been removed from the diagnostic criteria, which means that AML-MR includes only two types of AML now: AML with a history of MDN or MDN/MPN, and AML with at least one of the defining genetic abnormalities for AML-MR. AML with only morphologic evidence of multilineage dysplasia is no longer qualified for the diagnosis of AML-MR. The defining cytogenetic criteria for AML-MR have been revised as well, and the changes include the elimination of the balanced cytogenetic abnormalities, and the addition of defining somatic mutations: *ASXL1*, *BCOR*, *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *EZH2*, *STAG2*.

The diagnostic criteria for systemic mastocytosis have been revised. The major criterion stays the same, but the expression of CD30 has been added to the minor criterion of abnormal phenotype, and the presence of the active *KIT* mutation(s) other than codon 816 has also been accepted as one minor criterion. And for the minor criterion of basal serum tryptase, the tryptase level should be adjusted in patients with hereditary alpha-tryptasaemia (30).

UPDATED CYTOGENETIC/MOLECULAR GENETIC INFORMATION

Besides the above-mentioned changes and updates, there are numerous other updates involving almost every entity, covering from pathogenesis, and pathology to clinical features and prognosis. With tremendous advances in sequencing technology and large-scale integrated data analysis, new findings in genetic studies are abundant. These findings have led to the identification of many new subtypes and altered signaling pathways with potential for targeted therapy. There is no way to mention all the updates here, and the following are just a few examples.

Newly discovered recurrent cytogenetic abnormalities listed in *AML with other defined genetic abnormalities* include *RUNX1T3* (*CBFA2T3*)*::GLIS*, *KAT6A::CREBBP, FUS::ERG*, *MNX1::ETV6*, and *NPM1::MLF1*. Those listed in "B-LBL/L with other defined genetic abnormalities" include *DUX4* rearrangement, *MEF2D* rearrangement, *ZNF384* rearrangement, *NUTM1* rearrangements, *MYC* rearrangement, *PAX5alt* or *PAX5 p.P80R*. With more data accumulated, neoplasms with these new genetic abnormalities will very likely become separated subtypes in the next edition, and there will be more newly discovered genetic alterations listed here. Biallelic *TP53* alterations have been frequently found in MDNs, acute erythroid leukemia, and myeloid neoplasms post cytotoxic therapy, and they usually predict a worse prognosis (31). Gene mutations in the MAPK pathway are commonly seen in histiocytic neoplasms. *CXCR4* mutations are detected in a significant proportion of lymphoplasmacytic lymphoma cases, mostly concurrent with *MYD88* mutations, and the presence of them is associated with resistance to ibrutinib therapy (32). The mutational profiles of extranodal MZL (EMZL) and nodal MZL differ, and there are significant genetic differences among EMZLs arising in different anatomic sites (33). *STAT3* mutation is commonly seen in CD8+ T-LGLL and

gamma/delta T-LGLL, and it is associated with neutropenia and unfavorable overall survival; while *STAT5b* mutation is associated with a poor prognosis only in CD8+ T-LGLL but has no prognostic impact in CD4+ T-LGLL and gamma/delta T-LGLL (34).

CONCLUSION

Numerous changes and updates have been implemented in the 5th WHO-Hem to reflect our better understanding of these diseases through the tremendous amount of research work by many researchers and physicians. These changes and updates include revision of hierarchical classification structures, addition or deletion of categories/entities or subtypes, changes or revisions of nomenclature/terminology, changes or revisions of diagnostic criteria, and updates from many other aspects.

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