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The WHO Classification of Haematolymphoid Tumours

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INTRODUCTION

The World Health Organization (WHO) Classification of Tumours provides a definitive classification of all tumours, worldwide. This is essential to underpin the diagnosis and treatment of cancer, as well as research and education. Without it, clinical trial results could not be compared between countries, research results could not be evaluated collectively and epidemiological studies based on cancer registration would be impossible. It really is the basis of cancer science internationally.

HISTORICAL PERSPECTIVE

The 10th World Health Assembly, the governing body of the WHO, which today comprises 194 countries, directed the WHO to 'continue work on formulating international definitions of nomenclature and statistical classification'. This rather dry phrasing led to the International Classification of Disease series of coding systems and the WHO Classification of Tumours. Dr Leslie Sobin produced the first edition from 1967 to 1981, and the second over the course of 20 years, from 1982 to 2002. The late Dr Paul Kleihues then joined him to produce the 3rd edition from 2000 to 2005, reducing the time taken to produce the series to just 5 years from the previous 20 years. Unfortunately, the pace did not last: the 4th edition took from 2006 to 2018.

Prior to the 5th edition, we surveyed the readership and were told very clearly that the maximum tolerable update timing was 5 years: quite a challenge. We set about doing this, by converting the classification to a hierarchical taxonomy, entered into a database, and by paying careful attention to process management. The team leading this was another concern: the 4th edition had just four series editors (Drs Ohgaki, Bosman, Lakhani and Jaffe), who chose the editors for each volume, who then chose the authors. However well-intentioned and motivated the series editors, the likelihood of bias is obvious, as is the massive amount of work they took on. It is hardly surprising that the last edition took 12 years to complete. The fact that the 4th edition was so successful is a tribute to their abilities, but this could not continue given the explosion of knowledge that had to be processed for the 5th edition.

In 2017, the new head of the WHO Classification of Tumours, Dr Ian Cree, therefore set up an independent editorial board, the standing members of which are nominated by the major societies of pathology around the world [1–4]. This has since been expanded to include genetics and radiology, reflecting the increasingly multidisciplinary nature of the entire classification [5, 6]. Furthermore, expert members are also appointed to the editorial board for each of the volumes, and these, as well as authors, are selected by a process we know as 'informed bibliometrics', which involves looking at who is publishing substantive work in a given area over the last 5 years, informed by where they practice and by the opinion of standing members or, on occasion, international societies. This also meets the requirements of the WHO, which in May 2016 set up a 'framework for engagement with non-state actors' to ensure that organisations it dealt with were properly governed and worthy of participation.

The new approach in the 5th edition worked quite well across all blue books completed thus far. The only problem area was the classification of haematolymphoid tumours, which had previously used an ad-hoc 'clinical advisory committee' (CAC). Unfortunately, despite the fact that the CAC was a self-appointed group, it had nevertheless been allowed to take over the production of the 4th edition and to produce another 4th edition (revised) version 10 years later—and that volume took 3 years to produce. The CAC has been run by many of the same individuals with few changes for many years, and its selection process for new members is obscure. This contrasts with the WHO Classification of Tumours editorial board. Standing members can serve a maximum of two terms of 3 years each, for a total of 6 years. There was a previously unwritten rule in the WHO Classification of Tumours that experts can only serve as editors for two volumes, unless there are exceptional circumstances, and we have adopted that in writing for the 5th edition, with few exceptions.

The entire WHO classification is now held in a single database organised around an enhanced hierarchical taxonomy, which facilitates changes to the classification during the writing and editorial phases of production, and which mandates a systematic description of the shared characteristics of each tumour type. This also highlights the dearth of evidence in some areas—gaps in knowledge, which we hope will be addressed in future editions [7, 8]. Introductions to each chapter allow editors to identify what has changed from the previous edition and why, as well as giving a detailed explanation of choices made in the classification and their likely impact on diagnosis.

Quality-related issues identified to be addressed in the 5th edition related to the need to improve the quality of figures (an essential aspect, as we have switched to a two-column format with larger illustrations), the use of standardized international units [9, 10], HGNC/HGVS notation of genetics, avoidance of misleading terminology [11] and improved epidemiology. This has gained further importance as we continue to evolve the WHO Blue Books website (https://whobluebooks.iarc.fr), which permits even broader dissemination of the WHO classification and accessibility to it as a worldwide resource.

THE 5TH EDITION CLASSIFICATION OF HAEMATOLYMPHOID TUMOURS

The haematolymphoid tumours volume had the usual two editorial board meetings, the first in June 2021 and the second in November 2021. As published [3], the first of these meetings set the draft classification (table of contents) to which authorship groups were assigned. In line with the ethos of the 5th edition,

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these were multidisciplinary groups. When possible, they included hematopathology, genetics, and oncology/clinical haematology experts who have published on the subject within the last 5 years. Furthermore, in this volume, the expert editorial board was carefully selected to include broad multidisciplinary expertise, thereby infusing the effort from the beginning with a range of inputs that reflect current practice. With 420 experts involved in the volume as authors or editors, the range of expertise contributing to this volume is unprecedented. In addition, first, we sought public input on the initial outline (table of contents) of the classification by putting it out for public review and input on the WHO Blue Books website, with FAQs detailing the process followed. Feedback was reviewed by the editorial board, and changes were considered necessary.

The second editorial board considered the written evidence for each tumour type provided by the authorship groups. The scientific debate was to a very high standard and many issues were explored. In addition, a dedicated meeting was organised to receive expert clinical haematology/oncology input on the clinical implications of some of the changes introduced in this edition. The resulting 'to do' list took several months to complete and was followed by a final editorial board in a short format in March 2022. At the time of writing, the volume is now undergoing IARC editorial checking prior to technical editing. A beta version is expected to go online in July 2022, which allows feedback from users of the subscription website (https://tumourclassification.iarc.who.int/welcome/) with the publication of the printed book towards the end of 2022, all being well.

The outcome of this effort is another classification in the series that will help move the field forward by being based on a forward-looking multidisciplinary effort grounded in genetic advances, with an eye on worldwide applicability. An overview of the classification and its salient features are provided in the two excellent companion manuscripts, which cover the classification of myeloid and histiocytic/dendritic neoplasms [12] and the classification of lymphoid neoplasms [13].

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AUTHOR CONTRIBUTIONS

This paper was written by the author, and finalised with input from the WHO Classification of Tumours editorial board, to whom he is most grateful.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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REVIEW ARTICLE OPEN

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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

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The upcoming 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours is part of an effort to hierarchically catalogue human cancers arising in various organ systems within a single relational database. This paper summarizes the new WHO classification scheme for myeloid and histiocytic/dendritic neoplasms and provides an overview of the principles and rationale underpinning changes from the prior edition. The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. While a genetic basis for defining diseases is sought where possible, the classification strives to keep practical worldwide applicability in perspective. The result is an enhanced, contemporary, evidence-based classification of myeloid and histiocytic/dendritic neoplasms, rooted in molecular biology and an organizational structure that permits future scalability as new discoveries continue to inexorably inform future editions.

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INTRODUCTION

The World Health Organization (WHO) classification of tumours is an evidence-based classification of cancers occurring within various organ systems. It is a standard for diagnosis, research, cancer registries, and public health monitoring worldwide. For the first time since the inception of the classification over 60 years ago, the current series (5th edition) has been developed within a unified relational database framework that encompasses the entirety of human cancers. Tumours of each organ system and across volumes (blue books) are classified hierarchically within this novel framework along taxonomy principles and a set of non-negotiables that include process transparency, bibliographic rigor, and avoidance of bias [1, 2]. The development of the 5th edition is overseen by an editorial board that includes *standing members*—representatives from major medical and scientific organizations around the world—who oversee the entire series, in addition to *expert members* appointed for their leadership and contemporaneous expertise relevant to a particular volume [3]. The editorial board, in turn, identifies authors through an informed bibliometry process, with an emphasis on broad geographic representation and multidisciplinary expertise. By design, multidisciplinary author/editor groups (a total of 420 contributors) shared overlapping coverage of disease categories to ensure conceptual continuity and content harmonization. This approach reflects the ways in which the classification is meant to be implemented, with multidisciplinary input that emphasizes a holistic approach to patient management from diagnosis through disease monitoring.

The aim of this paper is to provide an overview of the new edition of the WHO classification for myeloid and histiocytic/dendritic tumours. The last edition of the haematolymphoid classification dates back to 2008 and was revised in 2017. An overview of the lymphoid tumours is provided in a companion manuscript [4].

The classification structure follows a lineage-based framework, flowing broadly from benign to malignant and branching down to category, family, type (disease/tumour), and subtype. Where possible, a triad of attributes was systematically applied and included: lineage + dominant clinical attribute + dominant

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biologic attribute. Lineage attribution rests on immunophenotyping with flow cytometry and/or immunohistochemistry. Dominant clinical attributes are general features of the untreated disease and include descriptors such as acute, chronic, cytopenia(s) (myelodysplasia) and cytosis(es) (myeloproliferation). Most biologic attributes include gene *fusions*, *rearrangements*, and *mutations*. Fusions are part of the nomenclature of types/subtypes when the identities of both implicated genes are required or often desirable criteria for diagnosis (e.g., *PML*::*RARA*). Rearrangements, a broad term that encompasses a range of structural genomic alterations leading to gene fusions, are part of the nomenclature of types/subtypes when there are multiple possible fusion partner genes of a biologically dominant gene (e.g., *KMT2A*). Of note, the use of the term rearrangements is maintained in the classification due to its wide usage across prior editions, although it is recognized that it is more appropriate for genomic modifications in genes consisting of various segments (e.g., immunoglobulin genes and T-cell receptor genes). A deliberate attempt is made to prioritize classifying tumour types based on *defining genetic abnormalities* where possible.

Emerging entities are listed as disease subtypes under a novel rubric of *other defined genetic alterations*. This is envisioned as a landing spot in the classification to incorporate new/rare entities whose recognition is increasing as high-throughput molecular diagnostic tools become more available. This approach replaces the assignment of provisional status to such entities. It is recognized that the diagnosis of such subtypes might not be feasible in all practice settings. A set of decision support guidelines was adopted to aid in determining what subtypes would qualify in this context; they include: (1) having distinct molecular or cytogenetic features driven by established oncogenic mechanisms; (2) not meeting subtype criteria under other tumour types with defining genetic abnormalities; (3) having distinct pathologic and clinical features, including - but not limited to - response to therapeutic interventions; and, (4) at least two quality peer-review publications by distinct investigator groups.

The application of this classification is predicated on integrating morphologic (cytology and histology), immunophenotypic, molecular and cytogenetic data. This is in line with previous editions, with expanded numbers of disease types and subtypes that are molecularly defined. It is hoped that the genetic underpinnings of the classification will prompt the provision of health resources to ensure that the necessary genetic testing platforms are available to peruse the full potential of the classification. Notwithstanding, the full published classification will include listing of essential diagnostic criteria that have the broadest possible applicability, particularly in limited resource settings. A further aid to broader applicability is the improved hierarchical structure of the classification, which permits reverting to family (class)-level definitions when detailed molecular genetic analyses may not be feasible; this approach is further elaborated on in the introduction of the blue book.

In line with the rest of the WHO 5th edition series, the classification of myeloid and histiocytic/dendritic neoplasms follows the Human Genome Organization Gene Nomenclature Committee recommendations, including the new designation of gene fusions using double colon marks (::) [5].

CLONAL HAEMATOPOIESIS

Clonal haematopoiesis (CH) refers broadly to the presence of a population of cells derived from a mutated multipotent stem/progenitor cell harbouring a selective growth advantage in the absence of unexplained cytopenias, haematological cancers, or other clonal disorders. The incidence of CH increases with age [6]. Substantial advances in understanding the molecular genetics and public health implications of CH took place since the last classification, including recognition of their association with increased overall mortality, cardiovascular diseases, and myeloid malignancies. More specific emerging associations, such as those characterizing the VEXAS (*v*acuoles, *E*1 enzyme, *X*-linked, *a*utoinflammatory, *s*omatic *UBA1* mutations) syndrome [7], represent manifestations of the interplay between inflammation and CH/myeloid neoplasia that are being gradually uncovered. Inclusion of CH in the classification represents a key inaugural effort to define and codify such myeloid precursor lesions.

Clonal haematopoiesis of indeterminate potential (CHIP) is defined in the classification as a term referring specifically to CH harbouring somatic mutations of myeloid malignancy-associated genes detected in the blood or bone marrow at a variant allele fraction (VAF) of ≥ 2% (≥4% for X-linked gene mutations in males) in individuals without a diagnosed haematologic disorder or unexplained cytopenia [8]. (Supplemental Data Table S1) The significance of variants detected at lower levels is unclear at present.

Clonal cytopenia of undetermined significance (CCUS) is defined as CHIP detected in the presence of one or more persistent cytopenias that are otherwise unexplained by haematologic or non-haematologic conditions and that do not meet diagnostic criteria for defined myeloid neoplasms. Cytopenia definitions are harmonized for CCUS, MDS, and MDS/MPN; they include Hb <13 g/dL in males and <12 g/dL in females for anaemia, absolute neutrophil count $<1.8 \times 10^9$/L for leukopenia, and platelets $<150 \times 10^9$/L for thrombocytopenia [9].

Summary Box:

- CH is recognized as a category of precursor myeloid disease state.
- CHIP and CCUS are formally defined.

MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative neoplasms (MPN) are listed in Table 1. The main types remain largely unchanged from the prior edition. Initial diagnostic evaluation of MPN continues to depend on close correlation between clinical features, molecular diagnostics, and usually morphologic evaluation of a trephine bone marrow biopsy. Most MPN patients are diagnosed in chronic phase (CP), which may progress into a blast phase (BP) associated with the accumulation of secondary cytogenetic and/or molecular aberrations.

Chronic myeloid leukaemia risk factors are refined, and accelerated phase is no longer required

Chronic myeloid leukaemia (CML) is defined by the *BCR*::*ABL1* fusion resulting from t(9;22)(q34;q11). The natural history of untreated CML before the introduction of targeted tyrosine kinase inhibitors (TKI) was biphasic or triphasic: an initial indolent CP followed by a blast phase (BP), with or without an intervening accelerated phase (AP). With TKI therapy and careful disease monitoring, the incidence of progression to advanced phase disease has decreased, and the 10-year overall survival rate for

Table 1. Myeloproliferative neoplasms.

Chronic myeloid leukaemia
Polycythaemia vera
Essential thrombocythaemia
Primary myelofibrosis
Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Juvenile myelomonocytic leukaemia
Myeloproliferative neoplasm, not otherwise specified

CML is 80–90% [10, 11]. The designation of AP has thus become less relevant, where resistance stemming from *ABL1* kinase mutations and/or additional cytogenetic abnormalities and the development of BP represent key disease attributes [12, 13]. Accordingly, AP is omitted in the current classification in favour of an emphasis on high risk features associated with CP progression and resistance to TKI. Criteria for BP include: (1) ≥20% myeloid blasts in the blood or bone marrow; or (2) the presence of an extramedullary proliferation of blasts; or (3) the presence of increased lymphoblasts in peripheral blood or bone marrow. The optimal cutoff for lymphoblasts and the significance of low-level B-lymphoblasts remain unclear and require additional studies.

Minor changes in diagnostic criteria for *BCR::ABL1*-negative myeloproliferative neoplasms

The classification retains an emphasis on distinguishing between polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) using diagnostic criteria established in previous editions, with minor refinements. Distinction between these types is based on integrating peripheral blood findings with molecular data and bone marrow morphologic evaluation findings, as none of these parameters alone provide sufficient diagnostic specificity.

Major diagnostic criteria for the diagnosis of PV include elevated haemoglobin concentration and/or haematocrit, accompanied by trilineage hyperplasia (panmyelosis), with pleomorphic mature megakaryocytes in the bone marrow, and NM_004972: JAK2 p.V617F or *JAK2* exon 12 mutations. As the determination of increased red cell mass with ^{51}Cr-labeled red cells has become uncommon in routine clinical practice, it has been removed as a diagnostic criterion. The diagnostic criteria of ET are well-established and have not changed.

Primary myelofibrosis (PMF) is characterized by a proliferation of abnormal megakaryocytes and granulocytes in the bone marrow, which is associated in fibrotic stages with a polyclonal increase in fibroblasts that drive secondary reticulin and/or collagen marrow fibrosis, osteosclerosis, and extramedullary haematopoiesis. Recognizing prefibrotic PMF remains necessary to separate it not only from ET and PV but also from fibrotic PMF [14]. The importance of serial monitoring of bone marrow fibrosis and spleen size using reproducible and standardized criteria remain pertinent, especially for patients receiving JAK1/2 inhibitors. PV and ET progress to AP (10-19% blasts) and BP (≥20% blasts) in a minority of cases, but leukaemic transformation is more frequent in PMF, and leukaemia-free survival is shorter in fibrotic than prefibrotic PMF [15, 16].

While *JAK2*, *CALR*, and *MPL* mutations are considered driver events, mutations in other genes – particularly *TET2*, *ASXL1*, and *DNMT3A* – are found in over half of patients with MPN. Mutations affecting splicing regulators (*SRSF2, SF3B1, U2AF1, ZRSR2*) and other regulators of chromatin structure, epigenetic functions and cellular signaling (e.g., *EZH2, IDH1, IDH2, CBL, KRAS, NRAS, STAG2, TP53*) are less common. These additional mutations are more frequent in PMF and advanced disease compared to PV and ET, and some are known to correlate with a poorer prognostic risk (e.g., *EZH2, IDH1, IDH2, SRSF2, U2AF1*, and *ASXL1* mutations in PMF).

Chronic neutrophilic leukaemia (CNL) is a *BCR::ABL1*-negative MPN characterized by sustained peripheral blood neutrophilia (white blood cell count (WBC) ≥ 25×10^9/L, with ≥80% segmented neutrophils and bands), bone marrow hypercellularity due to neutrophilic granulocyte proliferation, and hepatosplenomegaly. *CSF3R* mutations are common in this disease and detected in >60% of cases [17, 18].

Chronic eosinophilic leukaemia (CEL) is a multi-system disorder characterized by a sustained *clonal* proliferation of morphologically abnormal eosinophils and eosinophil precursors resulting in persistent hypereosinophilia in blood and bone marrow [19–21]. Several changes to the diagnostic criteria of CEL are introduced: (1) the time interval required to define sustained hypereosinophilia is reduced from 6 months to 4 weeks; (2) addition of requirement for both clonality and abnormal bone marrow morphology (e.g., megakaryocytic or erythroid dysplasia); and, (3) elimination of increased blasts (≥2% in peripheral blood or 5-19% in bone marrow) as an alternative to clonality. These criteria improve the distinction between CEL and entities such as idiopathic hypereosinophilic syndrome and hypereosinophilia of unknown significance [22]. As the criteria of CEL and its place relative to other disorders with eosinophilia have become well characterized, the qualifier "not otherwise specified" is no longer needed and has been omitted from the name.

As in prior editions, MPN, not otherwise specified (MPN-NOS) is a designation that should be reserved for cases with clinical, laboratory, morphologic, and molecular features of MPN but lacking diagnostic criteria of any specific MPN type or with features that overlap across distinct MPN types.

Juvenile myelomonocytic leukaemia is recognized as a myeloproliferative neoplasm of early childhood with frequent association with germline pathogenic gene variants

Juvenile myelomonocytic leukaemia (JMML) is a haematopoietic stem cell-derived myeloproliferative neoplasm of early childhood. The pathogenetic mechanism in at least 90% of cases involves unchecked activation of the RAS pathway. A diagnosis of JMML can be made by combining clinical, laboratory, and molecular criteria. Updates to diagnostic criteria include: (1) exclusion of *KMT2A* rearrangements; (2) elimination of monosomy 7 as a cytogenetic criterion; and, (3) emphasizing the significance of diagnostic molecular studies, particularly those aimed at demonstrating RAS pathway activation. The genetic background of JMML plays a major role in risk stratification and therapeutic approaches, with cases initiated by somatic mutations involving *PTPN11* and germline pathogenic variants associated with neurofibromatosis type 1 being the most aggressive types, while some cases associated with pathogenic germline *CBL* variants undergoing occasionally spontaneous remission. The inclusion of JMML under MPN reflects its molecular pathogenesis and underscores the virtual absence of stigmata of bona fide myelodysplastic neoplasia in this disease.

Summary Box:

- CML phases consolidated into chronic and blast phases, with emphasis on risk features in chronic phase.
- Diagnostic criteria of CEL are updated, and the qualifier NOS is omitted.
- JMML is categorized under myeloproliferative neoplasms.

MASTOCYTOSIS

Mastocytosis comprises rare heterogeneous neoplasms characterized by an accumulation of abnormal mast cells in various organs or tissues, typically driven by constitutive activation of the KIT receptor. The pathology of mastocytosis is complex, and clinical features span a broad spectrum that may be modulated by the presence of comorbidities. Significant comorbidities include IgE-dependent allergies, vitamin D deficiency, and psychiatric, psychological or mental problems. The classification continues to recognize three disease types: systemic mastocytosis (SM), cutaneous mastocytosis (CM) and mast cell sarcoma (MCS) [23]. (Table 2)

A somatic point mutation in the *KIT* gene at codon 816 is detected in >90% of patients with SM. Other rare activating *KIT* alterations include mutations in the extracellular (e.g., deletion of codon 419 on exon 8 or A502_Y503dup in exon 9), transmembrane (e.g., NM_000222:KIT p.F522C), or juxtamembrane (e.g., NM_000222:KIT p.V560G) domains, detected in <1% of advanced

SM cases but enriched in cases of indolent SM. Most patients with advanced SM and NM_000222:*KIT* p.D816V have additional somatic mutations involving most frequently *TET2, SRSF2, ASXL1, RUNX1*, and *JAK2*. An associated haematologic (usually myeloid) neoplasm may be detected in these patients [24].

Diagnostic criteria for SM have been modified. Namely, expression of CD30 and the presence of any *KIT* mutation causing ligand-independent activation have been accepted as minor diagnostic criteria. Basal serum tryptase level >20 ng/ml, which should be adjusted in case of hereditary alpha-tryptasaemia, is a minor SM criterion [25]. In addition, bone marrow mastocytosis is now a separate subtype of SM characterized by absence of skin lesions and B-findings and a basal serum tryptase below 125 ng/ml. Classical B-findings ('burden of disease') and C-findings ('cytoreduction-requiring') have undergone minor refinements. Most notably, NM_000222:*KIT* p.D816V mutation with VAF ≥ 10% in bone marrow cells or peripheral blood leukocytes qualifies as a B-finding.

The classification recognizes well-differentiated systemic mastocytosis (WDSM) as a morphologic pattern that can occur in any SM subtype, characterized by round and well-granulated mast cells usually heavily infiltrating the bone marrow. In most patients with WDSM, *KIT* codon 816 mutation is not detected, and neoplastic mast cells are usually negative for CD25 and CD2 but positive for CD30 [26].

Table 2. Mastocytosis types and subtypes.

Cutaneous mastocytosis
Urticaria pigmentosa/Maculopapular cutaneous mastocytosis
Monomorphic
Polymorphic
Diffuse cutaneous mastocytosis
Cutaneous mastocytoma
Isolated mastocytoma
Multilocalized mastocytoma
Systemic mastocytosis
Bone marrow mastocytosis
Indolent systemic mastocytosis
Smoldering systemic mastocytosis
Aggressive systemic mastocytosis
Systemic mastocytosis with an associated haematologic neoplasm
Mast cell leukemia
Mast cell sarcoma

Note: Well-differentiated systemic mastocytosis (WDSM) represents a morphologic variant that may occur in any SM type/subtype, including mast cell leukaemia.

Summary Box:

- Diagnostic criteria for mastocytosis have been refined: CD30 and any *KIT* mutation are introduced as minor diagnostic criteria.
- Bone marrow mastocytosis is a new SM subtype.
- *KIT* D816V mutation with VAF ≥ 10% qualifies as a B-finding.

MYELODYSPLASTIC NEOPLASMS

New terminology and grouping framework

The classification introduces the term *myelodysplastic neoplasms* (abbreviated MDS) to replace myelodysplastic syndromes, underscoring their neoplastic nature and harmonizing terminology with MPN. These clonal haematopoietic neoplasms are defined by cytopenias and morphologic dysplasia. As indicated above, cytopenia definitions are adopted for consistency across CCUS, MDS, and MDS/MPN. Additionally, the recommended threshold for dysplasia is set at 10% for all lineages. MDS entities are now grouped as those having *defining genetic abnormalities* and those that are *morphologically defined*. (Table 3) It is posited that such reorganization enhances classification rigor by emphasizing genetically-defined disease types and ceding the prior emphasis on 'risk-based' grouping in the classification (based on blast percentage, ring sideroblasts, and number of lineages with dysplasia) in favour of more comprehensive risk-stratification

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

schemes such as the Revised International Prognostic Scoring System for MDS (IPSS-R) [27]. An additional modification is a clarified terminology to distinguish between MDS with *low* blasts (MDS-LB) and MDS with *increased* blasts (MDS-IB), while retaining longstanding cutoffs.

MDS with defining genetic abnormalities

Myelodysplastic neoplasms with defining genetic abnormalities are grouped together and include: *MDS with low blasts and isolated 5q deletion* (MDS-5q), *MDS with low blasts and SF3B1 mutation* (MDS-*SF3B1*), and *MDS with biallelic TP53 inactivation* (MDS-bi*TP53*). The latter supersedes MDS-5q and MDS-*SF3B1*.

The diagnostic criteria of MDS-5q have not changed. While recognized as factors that may potentially alter the biology and/or prognosis of the disease, the presence of *SF3B1* or a *TP53* mutation (not multi-hit) does not per se override the diagnosis of MDS-5q.

Recent studies have identified MDS-*SF3B1* as a distinct disease type that includes over 90% of MDS with ≥5% ring sideroblasts [28]. The term *MDS with low blasts and ring sideroblasts* is retained as an acceptable alternative to be used for cases with wild-type *SF3B1* and ≥15% ring sideroblasts. This permits inclusion of rare MDS cases harbouring driver mutations in other RNA splicing components.

Pathogenic *TP53* alterations of any type (sequence variations, segmental deletions and copy neutral loss of heterozygosity) are detected in 7-11% of MDS [29–31]. Among these, about two-thirds of patients have multiple *TP53* hits (multi-hit), consistent with biallelic *TP53* alterations [29]. Biallelic *TP53* (bi*TP53*) alterations may consist of multiple mutations or mutation with concurrent deletion of the other allele. This "multi-hit" mutational status results in a neoplastic clone that lacks any residual wild-type p53 protein. Clinical detection of biallelic *TP53* alterations is based on sequencing analysis (covering at least exons 4 to 11) [29, 32], often coupled with a technique to detect copy number status, usually fluorescence in situ hybridization with a probe set specific for the *TP53* locus on 17p13.1 and/or array techniques (e.g., comparative genomic hybridization or single nucleotide polymorphism arrays) [33]. Loss of genetic material at the *TP53* locus may also be inferred by next-generation sequencing [29]. A *TP53* VAF ≥ 50% may be regarded as presumptive (not definitive) evidence of copy loss on the trans allele or copy neutral loss of heterozygosity when a constitutional *TP53* variant can be ruled out. When two or more *TP53* mutations are detected, they usually affect both alleles [29] and can be considered a multi-hit status. Over 90% of patients with MDS-bi*TP53* have complex, mostly very complex (>3), karyotype [29, 30] and thus are regarded as very high risk in IPSS-R [27]. Additional studies are needed to determine whether bi*TP53* status is per se AML-defining, a point for consideration in future editions. Notwithstanding, published data suggests that MDS-bi*TP53* may be regarded as AML-equivalent for therapeutic considerations [29, 30].

MDS, morphologically defined

Hypoplastic MDS (MDS-h) is listed as a distinct MDS type in this edition. Long recognized as having distinctive features, MDS-h is associated with a T-cell mediated immune attack on haematopoietic stem and progenitor cells, along with oligoclonal expansion of CD8 + cytotoxic T-cells overproducing IFNγ and/or TNFα. Several features overlap across the triad of MDS-h, paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia (AA), including an association with CH [34–36]. Many patients with MDS-h have sustainable responses to agents used in patients with AA (i.e., anti-thymocyte globulin, ATG). As such, an emphasis is placed on careful morphologic evaluation, typically requiring trephine biopsy evaluation in addition to evaluation of bone marrow smears and touch preparations, and detection of mutations and/or clonal cytogenetic abnormalities. Individuals with germline pathogenic variants in *GATA2*, *DDX41*, Fanconi anaemia (FA) or telomerase complex genes can have hypoplastic bone marrow and evolve to MDS and/or AML and do not respond to immunosuppressive treatment.

As the number of dysplastic lineages is usually dynamic and often represents clinical and phenotypic manifestation of clonal evolution – rather than per se defining a specific MDS type, the distinction between single lineage and multilineage dysplasia is now considered optional. The updated MDS classification scheme and the incorporation of CCUS in the classification obviates the need for "NOS" or "unclassifiable" attributes. Specifically, MDS, unclassifiable, which was present in the prior edition, is removed.

The boundary between MDS and AML is softened, but the 20% blast cutoff to define AML is retained

Reassessment of the bone marrow blast percentage defining the boundary of MDS-IB2 and AML has been advocated for several cogent reasons and in view of novel therapeutic approaches that show efficacy in patients currently classified as MDS or AML with 10-30% myeloid blasts [37–39]. Salient practical challenges underpinning arguments for such a reassessment include: (1) any blast-based cutoff is arbitrary and cannot reflect the biologic continuity naturally inherent in myeloid pathogenic mechanisms; (2) blast enumeration is subject to sampling variations/error and subjective evaluation; and, (3) no gold standard for blast enumeration exists, and orthogonal testing platforms can and often do produce discordant results. The pros and cons of merging MDS-IB2 with AML and adopting a 10% cutoff for what would be called MDS/AML were explored in multidisciplinary expert discussions and at editorial board meetings in the course of producing this classification. Lowering the blast cutoff to define AML was felt to suffer from the same challenges listed above and would merely replace one cutoff with another. Further, an arbitrary cutoff of 10% blasts to define AML (even if qualified as MDS/AML or AML/MDS) carries a risk of overtreatment. Accordingly, a balanced approach was adopted by eliminating blast cutoffs for most AML types with defining genetic alterations but retaining a 20% blast cutoff to delineate MDS from AML. Notwithstanding, there was broad agreement that MDS-IB2 may be regarded as AML-equivalent for therapeutic considerations and from a clinical trial design perspective when appropriate.

Childhood myelodysplastic neoplasms: Enhanced specificity of disease terminology introduced

Childhood MDS is a clonal haematopoietic stem cell neoplasm arising in children and adolescents (<18 years of age) leading to ineffective haematopoiesis, cytopenia(s), and risk of progression to AML. The annual incidence is 1-2 per million children, with 10-25% presenting with increased blasts. JMML, myeloid proliferations associated with Down syndrome, and MDS post cytotoxic therapy are excluded from this group and belong elsewhere in the classification. The qualifying term *childhood* MDS emphasizes that this category of myeloid neoplasms is biologically distinct from that seen in adults [40, 41], underscoring the need to further elucidate its pathogenesis which remains incompletely understood

Childhood MDS with low blasts (cMDS-LB) replaces the former term "refractory cytopenia of childhood (RCC)". It includes two subtypes: childhood MDS with low blasts, hypocellular; and, childhood MDS with low blasts, not otherwise specified (NOS). (Table 4) Exclusion of non-neoplastic causes of cytopenia such as infections, nutritional deficiencies, metabolic diseases, bone marrow failure syndromes (BMFS), and germline pathogenic variants remains an essential diagnostic prerequisite for childhood MDS with low blasts. Approximately 80% of cases show hypocellular bone marrow with features similar to severe aplastic anemia and other BMFS, requiring close morphologic examination to evaluate the distribution, maturation, and presence of dysplasia in haematopoietic lineages [42]. Some cytogenetic findings such

Table 4. Childhood myelodysplastic neoplasms (MDS).

	Blasts
Childhood MDS with low blasts	<5% BM; <2% PB
Hypocellular	
Not otherwise specified	
Childhood MDS with increased blasts	5–19% BM; 2–19% PB

BM bone marrow, *PB* peripheral blood.

as monosomy 7, 7q deletion, or complex karyotype are associated with an increased risk of progression to AML and typically treated with haematopoietic stem cell transplantation, while cases with normal karyotype or trisomy 8 can have an indolent course.

Childhood MDS with increased blasts (cMDS-IB) is defined as having ≥5% blasts in the bone marrow or ≥2% blasts in the peripheral blood. The genetic landscape of cMDS-IB and cMDS-LB is similar, and they both differ from MDS arising in adults. Acquired cytogenetic abnormalities and RAS-pathway mutations are more common in cMDS-IB compared to cMDS-LB [43, 44].

Summary Box:

- Myelodysplastic syndromes renamed myelodysplastic neoplasms (abbreviated MDS).
- MDS genetic types updated to include MDS-5q, MDS-*SF3B1* and MDS-bi*TP53*
- Hypoplastic MDS (MDS-h) is recognized as a distinct disease type.
- MDS with low blasts (MDS-LB) is a new term that enhances clarity.
- MDS with increased blasts (MDS-IB) is a new term that enhances clarity.
- Terminology of childhood MDS types is updated.

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

This category of myeloid neoplasms is defined by overlapping pathologic and molecular features of MDS and MPN, often manifesting clinically with various combinations of cytopenias and cytoses. The definition of cytopenias is the same as that for MDS. The classification includes major revisions in the diagnostic criteria of CMML and terminology changes for other MDS/MPN types. (Table 5)

Chronic myelomonocytic leukaemia diagnostic criteria, subtypes, and blast-based subgrouping criteria reflect diagnostic refinement and emphasize unifying characteristics

The prototype and most common MDS/MPN is chronic myelomonocytic leukaemia (CMML), which is characterized by sustained peripheral blood monocytosis and various combinations of somatic mutations involving epigenetic regulation, spliceosome, and signal transduction genes. Diagnostic criteria are revised to include prerequisite and supporting criteria. (Table 6) The first prerequisite criterion is persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis. Namely, the cutoff for absolute monocytosis is lowered from 1.0 ×10^9/L to 0.5 ×10^9/L to incorporate cases formerly referred to as oligomonocytic CMML [45–47]. To enhance diagnostic accuracy when absolute monocytosis is ≥0.5 ×10^9/L but <1.0 ×10^9/L, detection of one of more clonal cytogenetic or molecular abnormality and documentation of dysplasia in at least one lineage are required. Abnormal partitioning of peripheral blood monocyte subsets is introduced as a new supporting criterion [48, 49]. Additional studies are needed to determine the optimal approach to classifying individuals with unexplained clonal monocytosis [50] who do not fit the new diagnostic criteria of CMML.

Two disease subtypes with salient clinical and genetic features are now formally recognized based on WBC: *myelodysplastic* CMML (MD-CMML) (WBC < 13 × 10^9/L) and *myeloproliferative* CMML (MP-CMML) (WBC ≥ 13 × 10^9/L). MP-CMML is commonly associated with activating RAS pathway mutations and adverse clinical outcomes [51]. The blast-based subgroup of CMML-0 (<2% blasts in blood and <5% blasts in bone marrow) introduced in the previous edition has been eliminated in view of evidence that its addition provides no or limited prognostic significance [52, 53].

Table 5. Myelodysplastic/myeloproliferative neoplasms.

Chronic myelomonocytic leukaemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Atypical chronic myeloid leukaemia is renamed MDS/MPN with neutrophilia, and other terminology updates

Diagnostic criteria for other MDS/MPN types were largely unchanged. The term *MDS/MPN with neutrophilia* replaces the term atypical CML. This change underscores the MDS/MPN nature of the disease and avoids potential confusion with CML. MDS/MPN with ring sideroblasts and thrombocytosis is redefined based on *SF3B1* mutation and renamed *MDS/MPN with SF3B1 mutation and thrombocytosis*. The term MDS/MPN with ring sideroblasts and thrombocytosis has been retained as an acceptable term to be used for cases with wild-type *SF3B1* and ≥15% ring sideroblasts. MDS/MPN, unclassifiable is now termed *MDS/MPN, not otherwise specified*; this is in line with an intentional effort to remove the paradoxical qualifier "unclassifiable" from the entire classification.

Summary Box:

- CMML diagnostic criteria undergo major revisions, including lowering the cutoff for absolute monocytosis, adopting MD-CMML and MP-CMML subtypes, and eliminating CMML-0.
- Atypical chronic myeloid leukaemia renamed MDS/MPN with neutrophilia.
- MDS/MPN with ring sideroblasts and thrombocytosis redefined based on *SF3B1* mutation and renamed MDS/MPN with *SF3B1* mutation and thrombocytosis.

ACUTE MYELOID LEUKAEMIA

Enhanced grouping framework permitting scalable genetic classification and deemphasizing blast enumeration where relevant

The classification of AML is re-envisioned to emphasize major breakthroughs over the past few years in how this disease is understood and managed. Foremost is the separation of AML with defining genetic abnormalities from AML defined by differentiation. (Table 7) The latter eliminates the previously confusing use of the term AML NOS, under which types based on differentiation were listed. Another key change, as indicated above, is the elimination of the 20% blast requirement for AML types with defining genetic abnormalities (with the exception of AML with *BCR::ABL1* fusion and AML with *CEBPA* mutation). Removal of the blast cutoff requires correlation between morphologic findings and the molecular genetic studies to ensure that the defining abnormality is driving the disease pathology. This approach was deemed more appropriate than assigning another arbitrary lower bone marrow blast cutoff. A third component of the new structure is the introduction of a section on AML with *other defined genetic alterations*, a landing spot for new and/or uncommon AML subtypes that may (or may not) become defined types in future editions of the classification. As such, the overall AML classification structure continues to emphasize integration of clinical, molecular/genetic, and pathologic parameters and emphasis on clinicopathologic judgement.

Table 6. Diagnostic criteria of chronic myelomonocytic leukaemia.

Prerequisite criteria
1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]
Supporting criteria
1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]
Requirements for diagnosis
- Pre-requisite criteria must be present in all cases.
- If monocytosis is ≥ 1 × 10^9/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and <1 × 10^9/L: supporting criteria 1 and 2 must be met.
Subtyping criteria
- Myelodysplastic CMML (MD-CMML): WBC < 13 × 10^9/L
- Myeloproliferative CMML (MP-CMML): WBC ≥ 13 × 10^9/L
Subgrouping criteria (based on percentage of blasts and promonocytes)
CMML-1: <5% in peripheral blood and <10% in bone marrow
CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow

[a]Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes.
[b]Myeloproliferative neoplasms (MPN) can be associated with monocytosis at presentation or during the course of the disease; such cases can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or high burden of MPN-associated mutations (*JAK2, CALR* or *MPL*) tends to support MPN with monocytosis rather than CMML.
[c]Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.
[d]Morphologic dysplasia should be present in ≥10% of cells of a haematopoietic lineage in the bone marrow.
[e]Based on detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

AML with defining genetic abnormalities

While the classification retains much of the established diagnostic criteria for AML with *PML*::*RARA*, AML with *RUNX1*::*RUNX1T1*, and AML with *CBF*::*MYH11*, increased recognition of the importance of highly sensitive measurable residual disease (MRD) evaluation techniques, and the impact of concurrent molecular alterations reflect factors that impact patient management and therapeutic decisions in current practice. Namely, prognostic factors have expanded from *KIT* mutations, which are still relevant, to include additional cytogenetic features and MRD status post induction. The diagnostic criteria of AML with *DEK*::*NUP214* and AML with *RBM15*::*MRTFA* (formerly *RBM15*::*MKL1*) have also remained largely unchanged.

AML with *BCR*::*ABL1* and AML with *CEBPA* mutation are the only disease types with a defined genetic abnormality that require at least 20% blasts for diagnosis. The blast cutoff requirement is needed for the former to avoid overlap with CML. Distinguishing AML with *BCR*::*ABL1* from initial myeloid blast phase of CML can be challenging, and additional evidence continues to be needed to better characterize this AML type. There is insufficient data to support any change in the blast cutoff criterion for AML with *CEBPA* mutation [54, 55].

Three AML types with characteristic rearrangements involving *KMT2A, MECOM*, and *NUP98* are recognized. A blast count under 20% is acceptable based on studies demonstrating that patients with <20% blasts (MDS) and any of these rearrangements have clinical features that resemble those with higher blast counts. It is important to note that rearrangements involving these three genes, particularly *NUP98*, may be cryptic on conventional karyotyping. *AML with KMT2A rearrangement* is the new term that replaces "AML with t(9;11)(p22;q23); *KMT2A-MLLT3*". More than 80 *KMT2A* fusion partners have been described, with *MLLT3, AFDN, ELL*, and *MLLT10* being most common. While not required, the identification of the fusion partner is desirable since it could provide prognostic information and may impact disease monitoring. Adult patients often present with high blast counts, usually with monocytic differentiation. In children particularly, AML with *KMT2A*::*MLLT3* and *KMT2A*::*MLLT10* show megakaryoblastic differentiation and/or low blast counts in bone marrow aspirate smears.

AML defined by mutations include AML with *NPM1* and AML with *CEBPA* mutation. AML with *NPM1* mutation can be diagnosed irrespective of the blast count, albeit again with emphasis on judicious clinicopathologic correlation. This approach aligns with data showing that cases previously classified as MDS or MDS/MPN with *NPM1* progress to AML in a short period of time. Similar data have emerged from patients with CH who acquire *NPM1* mutation. The definition of AML with *CEBPA* mutation has changed to include biallelic (biCEBPA) as well as single mutations located in the basic leucine zipper (bZIP) region of the gene (smbZIP-*CEBPA*). The favourable prognosis associated with smbZIP-*CEBPA* has been demonstrated in cohorts of children and adults up to 70 years old. *RUNX1* mutations in AML overlap with such a broad range of defining molecular features that it was determined to lack enough specificity to define a standalone AML type.

Table 8. Cytogenetic and molecular abnormalities defining acute myeloid leukaemia, myelodysplasia-related.

Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

Several changes were introduced to the entity formerly designated AML with myelodysplasia-related changes, now called *AML, myelodysplasia-related* (AML-MR). This AML type is defined as a neoplasm with ≥20% blasts expressing a myeloid immunophenotype and harboring specific cytogenetic and molecular abnormalities associated with MDS, arising *de novo* or following a known history of MDS or MDS/MPN. Key changes include: (1) removal of morphology alone as a diagnostic premise to make a diagnosis of AML-MR; (2) update of defining cytogenetic criteria; and, (3) introduction of a mutation-based definition based on a set of 8 genes – *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*, > 95% of which are present specifically in AML arising post MDS or MDS/MPN [56, 57]. The presence of one or more cytogenetic or molecular abnormalities listed in Table 8 and/or history of MDS or MDS/MPN are required for diagnosing AML-MR.

AML with *other defined genetic alterations* represents a landing spot for new, often rare, emerging entities whose recognition is desirable to determine whether they might constitute distinct types in future editions. At present, subtypes under this heading include AML with rare genetic fusions.

AML defined by differentiation

This AML family includes cases that lack defining genetic abnormalities. (Table 9) It is anticipated that the number of such cases will diminish as discoveries provide novel genetic contexts for their classification. Notwithstanding, categorizing AML cases lacking defining genetic abnormalities based on differentiation offers a longstanding classification paradigm with practical, prognostic, and perhaps therapeutic implications.

The classification includes an updated comprehensive framework of differentiation markers and criteria, harmonized with those of mixed-phenotype acute leukaemia (MPAL) and early T-precursor lymphoblastic leukaemia/lymphoma (ETP-ALL) (see section below on acute leukaemia of ambiguous lineage). Indeed, the recent identification of *BCL11B* rearrangements in MPAL T/Myeloid, ETP-ALL, acute leukaemia of ambiguous lineage (ALAL) and a subset of AML with minimal differentiation suggests a biologic continuum across these entities, a finding with likely implications on future editions of the classification [58–61].

Acute erythroid leukaemia (AEL) (previously pure erythroid leukaemia, an acceptable related term in this edition) is a distinct AML type characterized by neoplastic proliferation of erythroid cells with features of maturation arrest and high prevalence of biallelic *TP53* alterations. Diagnostic criteria include erythroid predominance, usually ≥80% of bone marrow elements, of which ≥30% are proerythroblasts (or pronormoblasts). The occurrence of AEL cases in which nucleated erythroid cells constitute less than 80% of bone marrow cellularity is recognized; such cases share the same clinicopathologic features of other AEL [62, 63]. The central role that biallelic *TP53* mutations play in this aggressive AML type is underscored [64, 65]. The diagnosis of AEL supersedes AML-MR. *De novo* AEL and cases that arise following MDS or MDS/MPN share distinctive morphologic features, with prominent proerythroblast proliferation. Proerythroblast have been shown to play an important role in treatment resistance and poor prognosis in AML patients [66, 67].

Several molecular drivers can give rise to acute megakaryoblastic leukaemia (AMKL), which arises within three clinical groups: children with Down syndrome, children without Down syndrome, and adults. Immunophenotyping and detection of markers of megakaryocytic differentiation are required to make a diagnosis of AMKL and detect the newly described "RAM immunophenotype", which correlates with *CBFA2T3*::*GLIS2*, a subtype of *AML with other defined genetic alterations*.

Myeloid sarcoma

Myeloid sarcoma represents a unique tissue-based manifestation of AML or transformed MDS, MDS/MPN, or MPN. Cases of *de novo* myeloid sarcoma should be investigated comprehensively, including cytogenetic and molecular studies, for appropriate classification and planning therapy. Molecular alterations in myeloid sarcoma and concurrent bone marrow disease are concordant in ~70% of patients, suggesting that myeloid sarcoma may be derived from a common haematopoietic stem cell or precursor [68, 69]. Relevant gene mutations are detected in a subset of patients with morphologically normal-appearing bone marrow, suggesting low-level clonal myeloid disease or CH in the bone marrow [68, 70].

Summary Box:

- AML is arranged into two families: AML with *defining genetic abnormalities* and AML *defined by differentiation*. AML, NOS is no longer applicable.
- Most AML with defining genetic abnormalities may be diagnosed with <20% blasts.
- AML-MR replaces the former term AML "with myelodysplasia-related changes", and its diagnostic criteria are updated. AML transformation of MDS and MDS/MPN continues to be defined under AML-MR in view of the broader unifying biologic features.
- AML with rare fusions are incorporated as subtypes under AML with *other defined genetic alterations*.
- AML with somatic *RUNX1* mutation is not recognized as a distinct disease type due to lack of sufficient unifying characteristics.

SECONDARY MYELOID NEOPLASMS

A newly segregated category encompassing diseases that arise in the setting of certain known predisposing factors

Myeloid neoplasms that arise secondary to exposure to cytotoxic therapy or germline predisposition are grouped in this category. AML transformation of MPN is retained in the MPN category, while AML transformation of MDS and MDS/MPN is kept under AML-MR (see above). The framework of this disease category was redesigned with an eye towards two important areas: (1) providing a scalable structure for incorporating novel discoveries in the area of germline predisposition to myeloid neoplasia; (2) recognizing the dual importance of cataloguing myeloid neoplasms that arise following exposure to cytotoxic therapies for

Table 9. Differentiation markers and criteria for acute myeloid leukaemia (AML) types defined by differentiation.

Type	Diagnostic criteria*
AML with minimal differentiation	• Blasts are negative (<3%) for MPO and SBB by cytochemistry
	• Expression of two or more myeloid-associated antigens, such as CD13, CD33, and CD117
AML without maturation	• ≥3% blasts positive for MPO (by immunophenotyping or cytochemistry) or SBB and negative for NSE by cytochemistry
	• Maturing cells of the granulocytic lineage constitute <10% of the nucleated bone marrow cells
	• Expression of two or more myeloid-associated antigens, such as MPO, CD13, CD33, and CD117
AML with maturation	• ≥3% blasts positive for MPO (by immunophenotyping or cytochemistry) or SBB by cytochemistry
	• Maturing cells of the granulocytic lineage constitute ≥10% of the nucleated bone marrow cells
	• Monocyte lineage cells constitute < 20% of bone marrow cells
	• Expression of two or more myeloid-associated antigens, such as MPO, CD13, CD33, and CD117
Acute basophilic leukemia	• Blasts & immature/mature basophils with metachromasia on toluidine blue staining
	• Blasts are negative for cytochemical MPO, SBB, and NSE
	• No expression of strong CD117 equivalent (to exclude mast cell leukemia)
Acute myelomonocytic leukaemia	• ≥20% monocytes and their precursors
	• ≥20% maturing granulocytic cells
	• ≥3% of blasts positive for MPO (by immunophenotyping or cytochemistry)
Acute monocytic leukaemia	• ≥80% monocytes and/or their precursors (monoblasts and/or promonocytes)
	• <20% maturing granulocytic cells
	• Blasts and promonocytes expressing at least two monocytic markers including CD11c, CD14, CD36 and CD64, or NSE positivity on cytochemistry
Acute erythroid leukaemia	• ≥30% immature erythroid cells (proerythroblasts)
	• Bone marrow with erythroid predominance, usually ≥80% of cellularity
Acute megakaryoblastic leukaemia	• Blasts express at least one or more of the platelet glycoproteins: CD41 (glycoprotein IIb), CD61 (glycoprotein IIIa), or CD42b (glycoprotein Ib)[b]

*Shared diagnostic criteria include:
- ≥20% blasts in bone marrow and/or blood (except for acute erythroid leukaemia).
- Criteria for AML types with defined genetic alterations are not met.
- Criteria for mixed-phenotype acute leukaemia are not met (relevant for AML with minimal differentiation).
- Not fulfilling diagnostic criteria for myeloid neoplasm post cytotoxic therapy.
- No prior history of myeloproliferative neoplasm.

BM bone marrow, *MPO* myeloperoxidase, *NSE* nonspecific esterase, *PB* peripheral blood, *SBB* Sudan Black B.

clinical purposes as well as population health purposes. The latter factor is gaining increased recognition as cancer survival is prolonged and the incidence of late complications of therapy such as secondary myeloid neoplasia increases. An overarching principle in this context is the requirement to consider "post cytotoxic therapy" and "associated with germline [gene] variant" as disease attributes that should be added as qualifiers to relevant myeloid disease types whose criteria are fulfilled as defined elsewhere in the classification, e.g. *AML with KMT2A rearrangement post cytotoxic therapy* or *MDS with low blasts associated with germline RUNX1 variant*.

Myeloid neoplasms post cytotoxic therapy: introduction of more precise terminology and novel associations with new cytotoxic drug classes

As in previous editions, this category includes AML, MDS, and MDS/MPN arising in patients exposed to cytotoxic (DNA-damaging) therapy for an unrelated condition. The terminology and definitions of this disease category have been modified slightly to reflect an improved understanding of the risk that CH plays as a risk factor for myeloid neoplasia related particularly to the expansion of pre-existing clones secondary to selection pressures of cytotoxic therapy agents in an altered marrow environment [71]. Thus, the diagnosis of myeloid neoplasms post cytotoxic therapy (MN-pCT) entails fulfilment of criteria for a myeloid neoplasm in addition to a documented history of chemotherapy treatment or large-field radiation therapy for an unrelated neoplasm [72]. This would exclude CCUS, which by definition lacks sufficient support for morphologic dysplasia. Cases with a '*de novo* molecular signature' such as *NPM1* mutation and core-binding factor leukaemias should still be assigned to this category since the "*post cytotoxic therapy*" designation is based on the medical history, and the indication of the most specific diagnosis in the pathology report is recommended when possible. Exposure to PARP1 inhibitors is added as a qualifying criterion for MN-pCT, and methotrexate has been excluded. It is recommended that specification of the type of myeloid neoplasm is made when possible, with the appendix "post cytotoxic therapy" appended, e.g. CMML post cytotoxic therapy.

The majority of AML-pCT and MDS-pCT are associated with *TP53* mutations. The outcomes of such patients are generally worse with biallelic (multi-hit) *TP53* alterations, manifesting as ≥2 *TP53* mutations, or with concomitant 17p/*TP53* deletion or copy neutral LOH. Less frequent mutations involve genes such as *PPM1D* and DNA-damage response genes that may require additional work-up for germline predisposition.

Myeloid neoplasms associated with germline predisposition: A novel scalable model is introduced

Myeloid neoplasms associated with germline predisposition include AML, MDS, MPN, and MDS/MPN that arise in individuals with genetic conditions associated with increased risk of

Table 10. Subtypes of myeloid neoplasms associated with germline predisposition.

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
• Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
• Germline *DDX41* P/LP variant[a]
• Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
• Germline *GATA2* P/LP variant (GATA2-deficiency)
• Bone marrow failure syndromes
◦ Severe congenital neutropenia (SCN)
◦ Shwachman-Diamond syndrome (SDS)
◦ Fanconi anaemia (FA)
• Telomere biology disorders
• RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
• Down syndrome[a,b]
• Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
• Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
• Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a]Lymphoid neoplasms can also occur.
[b]See respective sections.
[c]Ataxia is not always present.
P pathogenic, *LP* likely pathogenic.

myeloid malignancies. Myeloid neoplasms arising in individuals with Fanconi anemia, Down syndrome, and RASopathies are discussed in separate dedicated sections. These diseases are now classified using a formulaic approach that couples the myeloid disease phenotype with the predisposing germline genotype, e.g., AML with germline pathogenic variants in *RUNX1*. The clinical manifestations of these diseases are grouped into three subtypes under which most germline predisposition conditions can be assigned. (Table 10) Genetic counseling and evaluation of family history is an expected component of the diagnostic evaluation of index patients. Myeloid proliferations associated with Down syndrome, typically associated with somatic exon 2 or 3 *GATA1* mutation, continue to encompass two clonal conditions that arise in children with constitutional trisomy 21: transient abnormal myelopoiesis (TAM), which is confined to the first 6 months of life and myeloid leukaemia of Down syndrome (ML-DS).

Summary Box:

- Myeloid neoplasms (MDS, MDS/MPN, and AML) *post cytotoxic therapy* (MN-pCT) require full diagnostic work up; the term replaces *therapy-related*.
- Exposure to PARP1 inhibitors is added as a qualifying criterion for MN-pCT.
- The diagnostic framework for myeloid neoplasm associated with germline predisposition is restructured along a scalable model that can accommodate future refinement and discoveries.

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK) are myeloid or lymphoid neoplasms driven by rearrangements involving genes encoding specific tyrosine kinases leading to fusion products in which the kinase domain is constitutively activated leading to cell signaling dysregulation that promotes proliferation and survival. (Table 11) These *BCR::ABL1*-negative diseases have long been recognized in view of their distinctive clinicopathologic features and sensitivity to TKI. They encompass a broad range of histologic types, including MPN, MDS, MDS/MPN, AML, and MPAL, as well as B- or T- lymphoblastic leukaemia/lymphoma (ALL). Extramedullary disease is common. While eosinophilia is a common and salient feature, it may be absent in some cases. From a diagnostic hierarchy standpoint, the diagnosis of MLN-TK supersedes other myeloid and lymphoid types, as well as SM. In some instances, defining genetic abnormalities of MLN-TK are acquired during course of a myeloid neoplasm such as MDS or MDS/MPN or at the time of MPN BP transformation. MLN-TK must be excluded before a diagnosis of CEL is rendered.

The majority of MLN-TK cases associated with *PDGFRA* rearrangements have cytogenetically cryptic deletion of 4q12 resulting in *FIP1L1::PDGFRA*, but *PDGFRA* fusions involving other partners are also identified. Cases with *PDGFRB* rearrangement result most commonly from t(5;12)(q32;p13.2) leading to *ETV6::PDGFRB*; however, more than 30 other partners have been identified. Cases with *FGFR1* rearrangement may manifest as chronic myeloid neoplasms or blast-phase disease of B-cell, T-cell, myeloid or mixed-phenotype origin, typically with associated eosinophilia. The characteristic cytogenetic feature is an aberration of chromosome 8p11. Detection of *JAK2* rearrangements leading to fusion products with genes other than *PCM1* have been recognized, supporting MLN-TK with *JAK2* rearrangement as a distinct type [73, 74]. Cases with *FLT3* fusion genes are particularly rare and result from rearrangements involving chromosome 13q12.2. They manifest as myeloid sarcoma with MPN features in the bone marrow or T-ALL with associated eosinophilia, but disease features and phenotypic presentation may be variable and diverse. MLN-TK with *ETV6::ABL1* should be separated from B-ALL with *ETV6::ABL1* [75].

The natural history of MLN-TK with *PDGFRA* or *PDGFRB* has been dramatically altered by TKI therapy, particularly imatinib. In contrast, patients with *FGFR1*, *JAK2* and *FLT3* fusions and *ETV6::ABL1* have more variable sensitivity to available newer generation TKIs [73, 76]; in most cases, long-term disease-free survival may only be achievable with allogeneic haematopoietic stem cell transplantation.

Other less common defined genetic alterations involving tyrosine kinase genes have also been discovered, and these are listed as MLN-TK subtypes under *MLN-TK with other defined tyrosine kinase fusions* until further data is accrued [77, 78].

Summary Box:

- Family renamed myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK).
- Recognition of novel types with *JAK2* rearrangements, *FLT3* rearrangements, and *ETV6::ABL1* fusion.
- New scalable genetic framework introduced under MLN-TK with *other* defined tyrosine kinase fusions.

ACUTE LEUKAEMIAS OF MIXED OR AMBIGUOUS LINEAGE

Acute leukemia of ambiguous lineage (ALAL) and mixed-phenotype acute leukaemia (MPAL) are grouped under a single category in view of their overlapping clinical and

Table 11. Genetic abnormalities defining myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.

PDGFRA rearrangement
PDGFRB rearrangement
FGFR1 rearrangement
JAK2 rearrangement
FLT3 rearrangement
ETV6::ABL1 fusion
Other defined tyrosine kinase fusions:
ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET

immunophenotypic features, which in recent studies have been shown to also share common molecular pathogenic mechanisms. Here too, a framework for a molecular classification is laid by separating ALAL/MPAL with defining genetic abnormalities from those that are defined based on immunophenotyping only. (Table 12)

Two new subtypes of ALAL with defining genetic alterations are added. The first subtype is MPAL with *ZNF384* rearrangement, which commonly has a B/myeloid immunophenotype and is identified in ~50% of pediatric B/myeloid MPAL with fusion partners including *TCF3*, *EP300*, *TAF15*, and *CREBBP*. *ZNF384*-rearranged B/myeloid MPAL and B-ALL have similar transcriptional profile, suggesting a biological continuum [79]. The other subtype is ALAL with *BCL11B* rearrangement, which has a more heterogenous immunophenotype - identified in acute undifferentiated leukaemia (AUL) and ~20-30% of T/myeloid MPAL. *BCL11B* rearrangement is also identified in AML with minimal differentiation or without maturation and ~20-30% of ETP-ALL. [59–61, 80] These different types of acute leukaemias with stem cell, myeloid, and T-ALL features having *BCL11B* rearrangement in common suggests a biological continuum. Other genomic findings such as *PHF6* mutations and *PICALM::MLLT10* fusions are also enriched in MPAL, but more studies are needed.

The assignment of lineage by immunophenotyping is dependent on the strength of association between each antigen and the lineage being assessed. As a general principle, the closer the expression of an antigen is to either the intensity and/or pattern of expression seen on the most similar normal population, the more likely it reflects commitment to that lineage. For instance, variable myeloperoxidase expression with an intensity and pattern similar to that seen in early myeloid maturation is more strongly associated with myeloid lineage than uniform dim myeloperoxidase expression. In addition, demonstration of a coordinated pattern of expression of multiple antigens from the same lineage further improves the specificity of those antigens for lineage assignment, e.g. combined expression of CD19, CD22, and CD10 is more strongly associated with B lineage than each antigen individually. Given these principles, the immunophenotypic criteria to be used for lineage assignment in cases where a single lineage is not evident are revised. (Table 13)

Assessment of myeloperoxidase expression by cytochemistry and/or flow cytometry immunophenotyping plays a key role intersecting AML with minimal differentiation, T/myeloid MPAL, and ETP-ALL. Various groups have proposed flow cytometry thresholds for positive myeloperoxidase expression in acute leukaemia, ranging from 3 to 28% of blasts [81–83]. The 3% cutoff for myeloperoxidase, historically used for cytochemistry, was determined to have high sensitivity but poor specificity for general lineage assignment in acute leukaemia by flow cytometry [82, 83]. A threshold of >10% for myeloperoxidase positivity seems to improve specificity [81], but no consensus cutoff has been established.

Summary Box:

- Acute leukaemias of mixed or ambiguous lineage are arranged into two families: ALAL with *defining genetic abnormalities* and ALAL, *immunophenotypically defined*.
- Novel genetic findings are listed as subtypes under ALAL *with other defined genetic alterations* as additional data accrues.
- Lineage assignment criteria for MPAL are refined to emphasize principles of intensity and pattern.

HISTIOCYTIC/DENDRITIC CELL NEOPLASMS

These neoplasms are positioned in the classification after myeloid neoplasms in recognition of their derivation from common myeloid progenitors that give rise to cells of the monocytic/histiocytic/dendritic lineages. (Table 14) Key changes in the current edition of the classification include: (1) inclusion of clonal plasmacytoid dendritic cell (pDC) diseases in this category; (2) moving follicular dendritic cell sarcoma and fibroblastic reticular cell tumor to a separate category; and, (3) addition of Rosai-Dorfman disease (RDD) and ALK-positive histiocytosis as disease types. Indeed, neoplasms that arise from lymphoid stromal cells such as follicular dendritic cell sarcoma and fibroblastic reticular cell tumor are now appropriately classified under the new chapter of "stroma-derived neoplasms of lymphoid tissues" as detailed in the companion manuscript [4].

Plasmacytoid dendritic cell neoplasms: recognition of clonal proliferations detected in association with myeloid neoplasms and refinement/update of the diagnostic criteria for blastic plasmacytoid dendritic cell neoplasm

Mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm reflects recent data showing that these represent clonal proliferation of pDCs with low grade morphology identified in the context of a defined myeloid neoplasm. Clonal MPDCP cells accumulate in the bone marrow of patients with myeloproliferative CMML harbouring activating RAS pathway mutations [84]. Patients with AML can have clonally expanded pDCs (pDC-AML), which share the same mutational landscape as $CD34^+$ blasts, and frequently arise in association with *RUNX1* mutations [85, 86]. It is unknown whether the pathogenetic mechanisms leading to MPDCP in association with MDS or MDS/MPN and with AML are the same. The framework for diagnosing blastic plasmacytoid dendritic cell neoplasm remains largely the same, with emphasis on immunophenotypic diagnostic criteria. (Table 15)

Dendritic and histiocytic neoplasms: Rosai-Dorfman disease and ALK-positive histiocytosis are new entities in the classification

Much has been learned about the molecular genetics of histiocytoses/histiocytic neoplasms in recent years. These neoplasms, in particular Langerhans cell histiocytosis/sarcoma, Erdheim-Chester disease, juvenile xanthogranuloma, RDD and histiocytic sarcoma, commonly show mutations in genes of the MAPK pathway, such as *BRAF, ARAF, MAP2K1, NRAS* and *KRAS*, albeit with highly variable frequencies, indicating a unifying genetic landscape for diverse histiocytoses and histiocytic neoplasms. ALK-positive histiocytosis furthermore converges on the MAPK pathway, which is one of the signaling pathways mediating ALK activation [87, 88]. Insights on genetic alterations have significant treatment implications, because of availability of highly effective therapy targeting components of the activated signaling pathway, such as BRAF and MEK inhibitors [88–92].

For RDD, the distinctive clinicopathologic features with accumulation of characteristic S100-positive large histiocytes showing emperipolesis, coupled with frequent gain-of-function mutations in genes of the MAPK pathway indicating a neoplastic

process, provides a rationale for this inclusion and offers opportunities for targeted therapy [92–95].

ALK-positive histiocytosis, which shows a broad clinicopathologic spectrum unified by the presence of ALK gene translocation (most commonly *KIF5B*::*ALK*) and remarkable response to ALK-inhibitor therapy, has been better characterized in recent studies [88, 96]. The multisystem systemic form that typically occurs in infants, with involvement of liver, spleen and/or bone marrow, runs a protracted course but often resolves slowly, either spontaneously or with chemotherapy. Other multisystem and single-system cases occur in any age group, with involvement of two or more organs or one organ alone, respectively, most commonly central/peripheral nervous system and skin; the disease has a favourable outcome with systemic and/or surgical therapy [88, 97]. The histiocytes in ALK-positive histiocytosis can assume variable appearances including large oval cells, foamy cells and spindle cells, some with multinucleation (including Touton giant cells) or emperipolesis. That is, morphology is not entirely diagnostic, and overlaps extensively with that of juvenile xanthogranuloma and rarely RDD. Thus, it is recommended that ALK immunostaining be performed for histiocytic proliferations not conforming to defined entities, to screen for possible ALK-positive histiocytosis.

In most circumstances, classification of a dendritic cell/macrophage neoplasm as Langerhans cell histiocytosis/sarcoma, indeterminate dendritic cell tumor, interdigitating dendritic cell sarcoma or histiocytic sarcoma is straightforward. Nonetheless, there are rare cases that show overlap or hybrid features, defying precise classification [98, 99].

Among histiocytic neoplasms, a subset of cases occurs in association with or follow a preceding lymphoma/leukaemia, most commonly follicular lymphoma, chronic lymphocytic leukaemia and T- or B-ALL [100]. Since these histiocytic neoplasms usually exhibit the same clonal markers and/or hallmark genetic changes as the associated lymphoma/leukaemia, a "transdifferentiation" mechanism has been proposed to explain the phenomenon [99–101]. Furthermore, the histiocytic neoplasm and associated lymphoma/leukaemia often show additional genetic alterations exclusive to each component, suggesting that divergent differentiation or transdifferentiation occurs from a common lymphoid progenitor clone [100, 102, 103]. Histiocytoses are also sometimes associated with myeloproliferative neoplasms [104], sharing mutations with $CD34^+$ myeloid progenitors [105], and with CH [106].

Table 12. Acute leukaemias of ambiguous lineage.

Acute leukaemia of ambiguous lineage with defining genetic abnormalities
Mixed-phenotype acute leukaemia with *BCR*::*ABL1* fusion
Mixed-phenotype acute leukaemia with *KMT2A* rearrangement
Acute leukaemia of ambiguous lineage with other defined genetic alterations
Mixed-phenotype acute leukaemia with *ZNF384* rearrangement
Acute leukaemia of ambiguous lineage with *BCL11B* rearrangement
Acute leukaemia of ambiguous lineage, immunophenotypically defined
Mixed-phenotype acute leukaemia, B/myeloid
Mixed-phenotype acute leukaemia, T/myeloid
Mixed-phenotype acute leukaemia, rare types
Acute leukaemia of ambiguous lineage, not otherwise specified
Acute undifferentiated leukaemia

Summary Box:

- Histiocytic/dendritic cell neoplasms are regrouped and positioned to follow myeloid neoplasms in the classification scheme in view of their close ontogenic derivation.
- Mature pDC proliferation is redefined with an emphasis on recent data demonstrating shared clonality with underlying myeloid neoplasms. This framework is bound to evolve in future editions.
- Diagnostic criteria of BPDCN are refined.
- ALK-positive histiocytosis is introduced as a new entity.

GENETIC TUMOR SYNDROMES WITH PREDISPOSITION TO MYELOID NEOPLASIA

Fanconi anaemia is a heterogeneous disorder caused by germline variants in the BRCA-Fanconi DNA repair pathway (≥21 genes) resulting in chromosomal breakage and hypersensitivity to crosslinking agents used for diagnosis. Clinical features include congenital anomalies, bone marrow failure, and cancer predisposition [107]. The new classification distinguishes 5 haematologic categories depending on blast percentage,

Table 13. Lineage assignment criteria for mixed-phenotype acute leukaemia.

	Criterion
B lineage	
CD19 strong[a]	1 or more also strongly expressed: CD10, CD22, or CD79a[c]
or,	
CD19 weak[b]	2 or more also strongly expressed: CD10, CD22, or CD79a[c]
T lineage	
CD3 (cytoplasmic or surface)[d]	Intensity in part exceeds 50% of mature T-cells level by flow cytometry or, Immunocytochemistry positive with non-zeta chain reagent
Myeloid lineage	
Myeloperoxidase	Intensity in part exceeds 50% of mature neutrophil level
or,	
Monocytic differentiation	2 or more expressed: Non-specific esterase, CD11c, CD14, CD64 or lysozyme

[a]CD19 intensity in part exceeds 50% of normal B cell progenitor by flow cytometry.
[b]CD19 intensity does not exceed 50% of normal B cell progenitor by flow cytometry.
[c]Provided T lineage not under consideration, otherwise cannot use CD79a.
[d]Using anti-CD3 epsilon chain antibody.

Table 14. Dendritic cell and histiocytic neoplasms.

Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Other dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman disease
ALK-positive histiocytosis
Histiocytic sarcoma

Table 15. Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasm.

Expected positive expression:
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56
Expected negative markers:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase
Immunophenotypic diagnostic criteria:
-Expression of CD123 and one other pDC marker(*) in addition to CD4 and/or CD56.
or,
-Expression of any three pDC markers and absent expression of all expected negative markers.

cytopenia and chromosomal abnormalities [108]. Dysgranulopoiesis and dysmegakaryopoiesis are histologic indicators of progression [109]. Allogenic haematopoietic stem cell transplantation is efficacious.

The term RASopathies encompasses a diverse group of complex, multi-system disorders associated with variants in genes involved in the RAS mitogen-activating protein kinase (MAPK) pathway. Myeloid neoplasms in RASopathies involve MAPK hyperactivation, leading to myeloid cell proliferation [110]. Genomic analysis of *NF1*, *NRAS*, *KRAS*, *PTPN11*, and *CBL* from myeloid neoplasms of patients suspected of having a RASopathy is important and aids in the diagnosis of JMML in the majority of cases [111, 112]. Diagnostic criteria include pathogenic variants in genes associated with the RAS pathway and/or classic phenotype suggestive of a RASopathy [113].

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LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

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We herein present an overview of the upcoming 5th edition of the World Health Organization Classification of Haematolymphoid Tumours focussing on lymphoid neoplasms. Myeloid and histiocytic neoplasms will be presented in a separate accompanying article. Besides listing the entities of the classification, we highlight and explain changes from the revised 4th edition. These include reorganization of entities by a hierarchical system as is adopted throughout the 5th edition of the WHO classification of tumours of all organ systems, modification of nomenclature for some entities, revision of diagnostic criteria or subtypes, deletion of certain entities, and introduction of new entities, as well as inclusion of tumour-like lesions, mesenchymal lesions specific to lymph node and spleen, and germline predisposition syndromes associated with the lymphoid neoplasms.

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INTRODUCTION

Evidence-based classification of disease is fundamental for the treatment of individual patients, monitoring of global disease incidence, and investigating all aspects of disease causation, prevention and therapy. The World Health Organization (WHO) classification of lymphoid tumours has provided a global reference for the diagnosis of lymphoid neoplasms since its 3rd edition in 2001 [1] which was based on the R.E.A.L Classification developed by the International Lymphoma Study Group (ILSG) in the early 1990s [2]. The definitions laid down in the successive WHO classifications [3, 4] have not only been adopted for use by pathologists, clinicians, and basic and translational research scientists, but they have also been incorporated into the International Classification of Diseases (ICD) codes, and thereby serve as a global reference for epidemiological monitoring across national and international health policy organizations. In this article, we provide the conceptual framework and major developments in lymphoid neoplasms in the upcoming 5th edition of the WHO Classification of Haematolymphoid Tumours (WHO-HAEM5) scheduled to be published in 2022. An overview of myeloid neoplasms will be published separately.

The International Agency for Research on Cancer (IARC) initiated the process culminating in WHO-HAEM5 in 2018 by laying out the governance rules and classification principles for the entire 5th Edition series of the WHO classification of tumours, comprising 14 volumes, each dedicated to neoplasia of specific organ systems and/or clinical contexts (Paediatric Tumours and Genetic Tumour Syndromes). In 2021, expert members of the editorial board and authors were invited to contribute to WHO-HAEM5 based on their records of diagnostic and/or scientific expertise, regional

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representation, equity and lack of potential conflicts-of-interest. For most chapters, a multidisciplinary author team was formed including haematopathologists, haematologists, oncologists, geneticists, epidemiologists and molecular biologists. Experts from other disciplines, such as radiation oncologists and immunologists, were also involved where appropriate. Author teams worked "virtually", in close collaboration, further supported by regular online meetings with the editorial team despite (and possibly in part thanks to) the challenges encountered during the COVID-19 pandemic. In addition, major issues arising during the development of the classification were discussed, resolved and harmonized across entities, both within WHO-HAEM5 and across other WHO volumes that cover some of the same entities in different clinical and/or organ-specific contexts. This was accomplished via regular meetings among expert groups and further dedicated conferences, including a clinical forum with all clinicians involved in the WHO-HAEM5. Public consultation was sought on an initial classification draft. Final decisions were taken based on principles of evidence-based medicine.

The resulting WHO-HAEM5 is a systematic evolution of the prior classifications. To allow for continuity in daily practice and ongoing clinical trials, a relatively conservative approach was taken in making changes to nomenclature. The WHO-HAEM5, like all 5th Edition WHO tumour volumes, applies a hierarchical system for classification. That is, it organises diseases in order of increasing levels of specification: category (e.g., mature B-cell), family/class (e.g., large B-cell lymphomas), entity/type (e.g., diffuse large B-cell lymphoma, not otherwise specified) and subtype (e.g., diffuse large B cell lymphoma, not otherwise specified, germinal center B-cell-like). Entities and subtypes have been formulated such that the implementation of the WHO-HAEM5 classification system is possible globally, in all settings. The WHO-HAEM5 recognizes the increasing importance of genetic and other molecular data in the evaluation of lymphoid neoplasia; however, consideration has also been given to the fact that the required diagnostic resources are not universally available. Thus, to facilitate a pragmatic approach to diagnosis while also encouraging the adoption of molecular testing where required, "essential" and "desirable" diagnostic criteria for each entity are defined in a hierarchical way. "Essential criteria" are minimal criteria to allow the diagnosis of an entity as universally as possible, although molecular criteria are inevitably included for some entities. "Desirable criteria" are those that aid in confirmation and refinement of the diagnosis, and usually require the application of advanced techniques. In circumstances where resources are not available to reach a definitive diagnosis of an entity (or when suboptimal quality or quantity of material is limiting), a diagnostic label based on the family name of that entity can be applied.

Provisional entities were not created in WHO-HAEM5 as these, by definition, lack sufficient evidence. Novel potential subtypes have been restrictively proposed for some entities, such as in Burkitt lymphoma, where besides the three traditional epidemiologic variants, the distinction of EBV-positive and EBV-negative Burkitt lymphoma subtypes is recommended.

The order of classification follows the traditional major subgrouping according to cell lineage, with precursor cell neoplasms followed by mature malignancies. Within a family, the entities are generally arranged in an order commencing with more indolent and progressing to increasingly aggressive ones. For the first time, in an effort to prevent the over-diagnosis of lymphoma and to improve the recognition of clinicopathologically distinct entities, non-neoplastic conditions mimicking lymphoma or representing an important differential diagnosis, have been included in WHO-HAEM5. Similarly, in light of the increasing clinical importance of germline tumour predisposition syndromes, which are frequently associated with lymphoid neoplasms, such as ataxia telangiectasia, dedicated chapters have been introduced. In addition, the rapid development in the understanding of lymphoid proliferations associated with inborn errors of immunity (primary immunodeficiencies) and acquired immune disorders justified significant updates, and these have been included in WHO-HAEM5.

The following sections represent an overview of the most significant changes made in WHO-HAEM5 compared with WHO-HAEM4R (Tables 1–3).

B-CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS

New addition to WHO-HAEM5: Tumour-like lesions with B-cell predominance

For the first time, the WHO 'Blue Book' on haematolymphoid tumours introduces tumour-like lesions, including five entities in a distinct class of **tumour-like lesions with B-cell predominance**. Castleman disease is not a single disease but rather three clinicopathologically distinct entities: unicentric Castleman disease, idiopathic multicentric Castleman disease, and KSHV/HHV8-associated multicentric Castleman disease. The diagnostic algorithm for the classification of Castleman disease requires an integrated approach, including histological, haematological, immunological, and clinical parameters [5–9]. Also included in this section is IgG4-related disease; IgG4-related lymphadenopathy has features that can overlap with Castleman disease. The fifth chapter covers other non-neoplastic B-cell predominant lymphoid proliferations involving lymph nodes and/or extranodal sites that can mimic lymphomas, including progressive transformation of germinal centers, infectious mononucleosis, florid reactive lymphoid hyperplasia/lymphoma-like lesion of the female genital tract, and systemic lupus erythematosus.

B-lymphoblastic leukaemias/lymphomas (B-ALL): New genetically defined entities and subtypes

Following the principles of 'essential' and 'desirable' diagnostic criteria outlined above, B-lymphoblastic leukaemia/lymphoma (B-ALL) can be diagnosed at the family/class level on morphology and immunophenotype alone as B-ALL, not further classified (NFC). Most entities can be classified based on broadly-available cytogenetic testing, although molecular genetic subtyping is required for some entities based on the current state-of-the-art. B-ALL NOS, is to be reserved for cases that cannot be classified even after comprehensive testing. The majority of precursor B-cell neoplasms are classified in WHO-HAEM5 according to ploidy changes, such as hyperdiploidy and hypodiploidy, as well as chromosomal rearrangements or the presence of other genetic drivers [10]. In most cases, well-known drivers underlie B-ALL pathogenesis: iAMP21, *BCR*::*ABL1* fusion, *KMT2A* rearrangements, *ETV6*::*RUNX1* fusion, *TCF3*::*PBX1* fusion or *IGH*::*IL3* fusion. The classification based on these groups remains largely unchanged from WHO-HAEM4R; however, the nomenclature focuses on the molecular events rather than cytogenetic alterations, to allow for the application of differing techniques for their detection (Table 1). Other minor updates reflect the incorporation of additional genetic findings and refinements in the definitions of entities based on shared gene expression features. The rare B-ALL with *TCF3*::*HLF* fusion has been added to WHO-HAEM5; it is distinct from B-ALL with *TCF3*::*PBX1* fusion and is characterized by a particularly aggressive behaviour [11, 12]. B-ALL with *BCR*::*ABL1*-like features is now an entity (previously a provisional entity), by definition sharing gene expression and phenotypic features of B-ALL with *BCR*::*ABL1* fusion; it is prevalent across all age groups [13, 14] and shows significant benefit from targeted therapies [15–17]. Similarly, advances in diagnostic methodologies have allowed identification of a new entity, B-ALL with *ETV6*::*RUNX1*-like features, the description of which follows the section on B-ALL with *ETV6*::*RUNX1* fusion [18].

Recent gene expression and sequencing studies have identified a number of novel genetic drivers that appear to confer distinct

Table 1. WHO Classification of Haematolymphoid Tumours, 5th edition: B-cell lymphoid proliferations and lymphomas.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with B-cell predominance	
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma	*Not previously included*
IgG4-related disease	*Not previously included*
Unicentric Castleman disease	*Not previously included*
Idiopathic multicentric Castleman disease	*Not previously included*
KSHV/HHV8-associated multicentric Castleman disease	Multicentric Castleman disease
Precursor B-cell neoplasms	
B-cell lymphoblastic leukaemias/lymphomas	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with iAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with *BCR*::*ABL1* fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
B-lymphoblastic leukaemia/lymphoma with *BCR*::*ABL1*-like features	B-lymphoblastic leukaemia/lymphoma, *BCR-ABL1*-like
B-lymphoblastic leukaemia/lymphoma with *KMT2A* rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged
B-lymphoblastic leukaemia/lymphoma with *ETV6*::*RUNX1* fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukaemia/lymphoma with *ETV6*::*RUNX1*-like features	*Not previously included*
B-lymphoblastic leukaemia/lymphoma with *TCF3*::*PBX1* fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-lymphoblastic leukaemia/lymphoma with *IGH*::*IL3 fusion*	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*
B-lymphoblastic leukaemia/lymphoma with *TCF3*::*HLF* fusion	*Not previously included*
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)
Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	(Same)
(Entity deleted)	B-cell prolymphocytic leukaemia
Splenic B-cell lymphomas and leukaemias	
Hairy cell leukaemia	(Same)
Splenic marginal zone lymphoma	(Same)
Splenic diffuse red pulp small B-cell lymphoma	(Same)
Splenic B-cell lymphoma/leukaemia with prominent nucleoli	*Not previously included* (encompassing hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma	
Lymphoplasmacytic lymphoma	(Same)
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	(Same)
Primary cutaneous marginal zone lymphoma	*Not previously included (*originally included under "extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue")
Nodal marginal zone lymphoma	(Same)
Paediatric marginal zone lymphoma	(Same)
Follicular lymphoma	
In situ follicular B-cell neoplasm	In situ follicular neoplasia
Follicular lymphoma	(Same)
Paediatric-type follicular lymphoma	(Same)
Duodenal-type follicular lymphoma	(Same)

Table 1. continued

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Cutaneous follicle centre lymphoma	
Primary cutaneous follicle centre lymphoma	(Same)
Mantle cell lymphoma	
In situ mantle cell neoplasm	In situ mantle cell neoplasia
Mantle cell lymphoma	(Same)
Leukaemic non-nodal mantle cell lymphoma	(Same)
Transformations of indolent B-cell lymphomas	
Transformations of indolent B-cell lymphomas	*Not previously included*
Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with *IRF4* rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	*Not previously included* (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	*Not previously included*
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	*Not previously included*, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (*plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)*
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)
Burkitt lymphoma	
Burkitt lymphoma	(Same)
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas	
Primary effusion lymphoma	(Same)
KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation	
Hyperplasias arising in immune deficiency/dysregulation	*Not previously included*, encompassing non-destructive post-transplant lymphoproliferative disorders, among others
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation	*Not previously included*, encompassing polymorphic posttransplant lymphoproliferative disorders, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, among others
EBV-positive mucocutaneous ulcer	(Same)
Lymphomas arising in immune deficiency / dysregulation	*Not previously included*, encompassing monomorphic posttransplant lymphoproliferative disorders, classic Hodgkin lymphoma posttransplant lymphoproliferative disorders, lymphomas associated with HIV infection, among others
Inborn error of immunity-associated lymphoid proliferations and lymphomas	Lymphoproliferative diseases associated with primary immune disorders

Table 1. continued

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Hodgkin lymphoma	
Classic Hodgkin lymphoma	(Same)
Nodular lymphocyte predominant Hodgkin lymphoma	(Same)
Plasma cell neoplasms and other diseases with paraproteins	
Monoclonal gammopathies	
Cold agglutinin disease	*Not previously included*
IgM monoclonal gammopathy of undetermined significance	(Same)
Non-IgM monoclonal gammopathy of undetermined significance	(Same)
Monoclonal gammopathy of renal significance	*Not previously included*
Diseases with monoclonal immunoglobulin deposition	
Immunoglobulin-related (AL) amyloidosis	Primary amyloidosis
Monoclonal immunoglobulin deposition disease	Light chain and heavy chain deposition disease
Heavy chain diseases	
Mu heavy chain disease	(Same)
Gamma heavy chain disease	(Same)
Alpha heavy chain disease	(Same)
Plasma cell neoplasms	
Plasmacytoma	(Same)
Plasma cell myeloma	(Same)
Plasma cell neoplasms with associated paraneoplastic syndrome -POEMS syndrome -TEMPI syndrome -AESOP syndrome	(Same) Except AESOP syndrome *not previously included*

clinical, phenotypic and/or prognostic features. Considering emerging, yet limited, evidence for separating them in the future as potential novel entities, these new subtypes are subsumed under "B-ALL with other defined genetic abnormalities". These include B-ALL with *DUX4* [18, 19], *MEF2D* [20], *ZNF384* [21] or *NUTM1* [22] rearrangements, with *IG::MYC* fusion [23, 24], and with *PAX5*alt [25] or PAX5 p.P80R (NP_057953.1) [26] abnormalities. Intriguingly, B-ALL with *ZNF384* rearrangement, *DUX4* rearrangement or PAX5 p.P80R may show monocytic differentiation following therapy and even at diagnosis [27, 28], broadening concepts of the plasticity of leukemic lineages. This plasticity has important implications for disease management, including minimal residual disease (MRD) assessment [27].

Mature B-cell neoplasms

The category of mature B-cell neoplasms comprises 12 families. The hierarchical structure is outlined in Table 1.

Pre-neoplastic and neoplastic small lymphocytic proliferations: MBL and CLL/SLL remain; B-PLL is no longer recognized as an entity

This family comprises two entities: Monoclonal B-cell Lymphocytosis (MBL) and Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL). WHO-HAEM5 recognizes three subtypes of **monoclonal B-cell lymphocytosis (MBL)**:

a. **Low-count MBL or clonal B-cell expansion**: clonal CLL/SLL-phenotype B-cell count below 0.5×10^9/L with no other features diagnostic of B-lymphoproliferative disorder. The arbitrary threshold is based on the distribution of clonal B-cell counts in population studies compared to clinical cohorts [29].
b. **CLL/SLL-type MBL:** monoclonal CLL/SLL-phenotype B-cell count $\geq 0.5 \times 10^9$/L and total B-cell count less than 5×10^9/L with no other features diagnostic of CLL/SLL [30]. The threshold of less than 5×10^9/L is arbitrary but identifies a group with a very low likelihood of requiring treatment compared to individuals with B-cell counts between 5–10 x 10^9/L [31].
c. **non-CLL/SLL-type MBL:** ANY monoclonal non-CLL/SLL phenotype B-cell expansion with no symptoms or features diagnostic of another mature B-cell neoplasm. The majority of cases have features consistent with a marginal zone (MZ) origin [32].

All subtypes of MBL are clinically characterized by immune impairment with sub-optimal response to vaccinations and increased risk of infection [33–37]. In the diagnosis of **CLL**, CD5, CD19, CD20, CD23, and surface or cytoplasmic kappa and lambda light chains are regarded as essential markers, and CD10, CD43, CD79b, CD81, CD200 and ROR1 as additional targets useful in the differential diagnosis from other small B-cell lymphomas/leukaemias [38]. In addition to del(11q), del(13q), del(17p), and trisomy 12 assessment, *TP53* mutational analysis, immunoglobulin gene heavy chain variable (*IGHV)* region somatic hypermutation (SHM) analysis and B-cell receptor stereotype subset analysis (subset #2 configuration) are all essential for full prognostic evaluation of CLL/SLL [39–41]. Detection of karyotypic complexity and *BTK, PLCG2*, and *BCL2* mutation status all remain desirable additional investigations in the context of targeted therapy. *IGHV* mutation and *TP53* aberration status are both included in the CLL-international prognostic index (CLL-IPI) [42], along with age, clinical stage and beta 2-microglobulin level. The International Prognostic Score for early-stage CLL/SLL (IPS-E) includes *IGHV* mutation status, absolute lymphocyte count $>15 \times 10^9$/L, and presence of palpable lymph nodes [43]. In the setting of

Table 2. WHO Classification of Haematolymphoid Tumours, 5th edition: T-cell and NK-cell lymphoid proliferations and lymphomas.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with T-cell predominance	
Kikuchi-Fujimoto disease	*Not previously included*
Indolent T-lymphoblastic proliferation	*Not previously included*
Autoimmune lymphoproliferative syndrome	*Not previously included*
Precursor T-cell neoplasms	
T-lymphoblastic leukaemia/lymphoma	
T-lymphoblastic leukaemia / lymphoma, NOS	T-lymphoblastic leukaemia/lymphoma
Early T-precursor lymphoblastic leukaemia / lymphoma	Early T-cell precursor lymphoblastic leukaemia
(Entity deleted)	NK-lymphoblastic leukaemia/lymphoma
Mature T-cell and NK-cell neoplasms	
Mature T-cell and NK-cell leukaemias	
T-prolymphocytic leukaemia	(Same)
T-large granular lymphocytic leukaemia	T-cell large granular lymphocytic leukaemia
NK-large granular lymphocytic leukaemia	Chronic lymphoproliferative disorder of NK cells
Adult T-cell leukaemia/lymphoma	(Same)
Sezary syndrome	(Same)
Aggressive NK-cell leukaemia	(Same)
Primary cutaneous T-cell lymphomas	
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder	(Same)
Primary cutaneous acral CD8-positive lymphoproliferative disorder	Primary cutaneous acral CD8-positive T-cell lymphoma
Mycosis fungoides	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma	(Same)
Subcutaneous panniculitis-like T-cell lymphoma	(Same)
Primary cutaneous gamma/delta T-cell lymphoma	(Same)
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	(Same)
Primary cutaneous peripheral T-cell lymphoma, NOS	*Not previously included*
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas	
Indolent T-cell lymphoma of the gastrointestinal tract	Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	*Not previously included*
Enteropathy-associated T-cell lymphoma	(Same)
Monomorphic epitheliotropic intestinal T-cell lymphoma	(Same)
Intestinal T-cell lymphoma, NOS	(Same)
Hepatosplenic T-cell lymphoma	
Hepatosplenic T-cell lymphoma	(Same)
Anaplastic large cell lymphoma	
ALK-positive anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-positive
ALK-negative anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma	(Same)
Nodal T-follicular helper (TFH) cell lymphoma	
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
Other peripheral T-cell lymphomas	
Peripheral T-cell lymphoma, not otherwise specified	(Same)
EBV-positive NK/T-cell lymphomas	
EBV-positive nodal T- and NK-cell lymphoma	*Not previously included*

Table 2. continued

Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma, nasal-type
EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood	
Severe mosquito bite allergy	(Same)
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
Systemic EBV-positive T-cell lymphoma of childhood	(Same)

Table 3. WHO Classification of Haematolymphoid Tumours, 5th edition: Stroma-derived neoplasms of lymphoid tissues.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Mesenchymal dendritic cell neoplasms	
Follicular dendritic cell sarcoma	(Same)
EBV-positive inflammatory follicular dendritic cell sarcoma	Inflammatory pseudotumour-like follicular/fibroblastic dendritic cell sarcoma
Fibroblastic reticular cell tumour	(Same)
Myofibroblastic tumour	
Intranodal palisaded myofibroblastoma	*Not previously included*
Spleen-specific vascular-stromal tumours	
Splenic vascular-stromal tumours	
Littoral cell angioma	*Not previously included*
Splenic hamartoma	*Not previously included*
Sclerosing angiomatoid nodular transformation of spleen	*Not previously included*

transformation, use of the term "Richter transformation" is recommended over "Richter Syndrome".

B-prolymphocytic leukaemia (B-PLL) of WHO-HAEM4R is *no longer recognized* in WHO-HAEM5 in view of its heterogeneous nature. Cases that have been labeled as B-PLL include: (1) a variant of mantle cell lymphoma, characterized by presence of *IGH*::*CCND1;* (2) prolymphocytic progression of CLL/SLL, defined by CD5-positive non-mantle B-cell neoplasm with >15% prolymphocytes in the peripheral blood and/or bone marrow [44–47], and (3) other cases, now classified as "splenic B-cell lymphoma/leukaemia with prominent nucleoli".

Splenic B-cell lymphomas and leukaemias: The term "splenic B-cell lymphoma/ leukaemia with prominent nucleoli" replaces "hairy cell leukaemia variant" and "CD5-negative B-cell prolymphocytic leukaemia"

The splenic B-cell lymphoma and leukaemia family in WHO-HAEM5 includes hairy cell leukaemia (HCL), splenic B-cell lymphoma/leukaemia with prominent nucleoli (SBLPN), splenic diffuse red pulp small B-cell lymphoma (SDRPL) and splenic marginal zone lymphoma (SMZL) (Fig. 1). In contrast to WHO-HAEM4R, SBLPN and SDRPL are now separately classified, with a nomenclature change in the former. **Hairy cell leukaemia** is a mature B-cell neoplasm with distinctive clinicopathologic features and BRAF p.V600E (NP_004324.2) somatic mutation in ≥95% of cases [48]. Other splenic small B-cell lymphomas usually lack *BRAF* mutations.

The new entity **splenic B-cell lymphoma/leukaemia with prominent nucleoli (SBLPN)** replaces the previous term "hairy-cell leukaemia variant", in recognition that this proliferation is biologically distinct from HCL, although the leukaemic cells may partly resemble the "hairy cells" of HCL. Moreover, this entity also absorbs all cases previously termed CD5-negative B-prolymphocytic leukaemia (B-PLL) per WHO-HAEM4R. Although data from the literature cannot be directly extrapolated to the new class, it can be stated that SBLPN is rare, comprising approximately 0.4% of chronic lymphoid malignancies [49–53], and affects mainly elderly patients. The neoplastic cells have prominent nucleoli and are negative for HCL markers CD25, annexin A1, TRAP, and CD123. SBLPN is clinically more aggressive than HCL and resistant to cladribine as single-agent treatment. More recently improved sensitivity to cladribine in combinations with rituximab or bendamustine has been shown [49, 54–56].

Splenic diffuse red pulp small B-cell lymphoma (SDRPL) has some features overlapping with HCL and SBLPN but can be distinguished on careful evaluation of morphologic and immunophenotypic characteristics. A CD200 mean fuorescence intensity (MFI)/CD180 MFI ratio <0.5 on flow cytometry favours a diagnosis of SDRPL over HCL, SMZL, and SBLPN [57]. These entities can be best discriminated by pathologic examination of the spleen; in the absence of a splenectomy specimen, bone marrow examination shows characteristic features in SDRPL with a predominant intrasinusoidal pattern, while SMZL and SBLPN have a more diverse growth pattern in the bone marrow and HCL shows a typical diffuse pattern with reticulin fibrosis [58, 59]. In absence of a splenectomy specimen, however, the distinction is often not possible.

Lymphoplasmacytic lymphoma: IgM matters

WHO-HAEM5 recognizes two subtypes of **lymphoplasmacytic lymphoma (LPL)**, the most common being the IgM-LPL/Waldenström Macroglobulinaemia (WM) type. Non-WM type LPL represents around 5% of LPL and includes: (1) cases with IgG or IgA monoclonal proteins, (2) non-secretory LPL, and (3) IgM LPL without bone marrow involvement [60–65].

There are two molecular subsets of IgM-LPL/WM type based on the presence or absence of the MYD88 p.L265P (NP_002459.2) mutation, which is regarded as the hallmark driver mutation in the vast majority of LPL (>90%) [66–69]. Demonstration of the MYD88 p.L265P mutation may aid in the difficult differential diagnosis with nodal and extranodal marginal zone lymphomas (MZL) with plasmacytoid differentiation and plasma cell (multiple) myeloma.

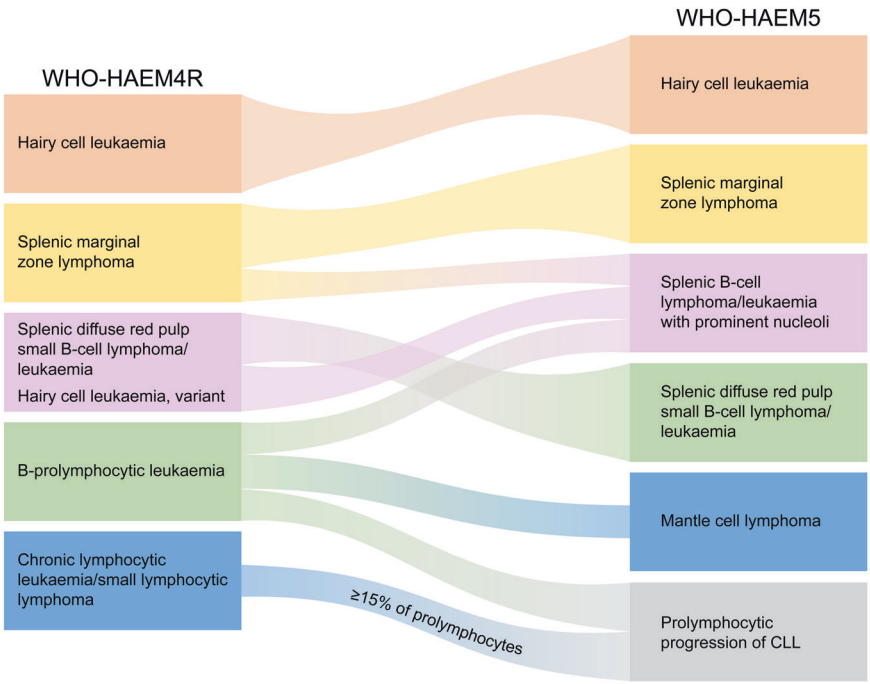

Fig. 1 Summary of the relationship between splenic B-cell lymphoma entities as named and defined in the revised 4th edition of the WHO classification (WHO-HAEM4R) and in the present 5th edition (WHO-HAEM5). Some cases previously classified as B-prolymphocytic leukaemia do represent (blastoid) mantle cell lymphoma (as was already indicated in WHO-HAEM4R) or prolymphocytic progression of CLL. Cases classified in WHO-HAEM4R as CLL/SLL with ≥ 15% of prolymphocytes are now classified as prolymphocytic progression of CLL, cases with <15% of prolymphocytes remain CLL/SLL in WHO-HAEM5. Remaining cases are now renamed as "splenic B-cell lymphoma/ leukaemia with prominent nucleoli" (SBLPN). This latter entity has absorbed cases formerly classified as hairy cell leukaemia variant (HCLv) and very rare cases of splenic marginal zone lymphoma with similar morphological features. It should be noted that the distinction between the various entities cannot always be made in the absence of a splenectomy specimen.

The two latter entities generally lack the MYD88 p.L265P mutation with the exception of rare cases of MZL. *CXCR4* mutations occur in up to 40% of all LPLs, usually concurrent with *MYD88* mutations. It is desirable to perform *CXCR4* mutational analysis for patients considered for treatment with a BTK inhibitor, since this genetic context is not only associated with shorter time to treatment, but especially with resistance to ibrutinib therapy [70].

Marginal zone lymphomas: cytogenetic and mutational profiles differ by anatomic site, and cutaneous MZL achieves independence

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL) and **nodal marginal zone lymphoma (NMZL)**, featured as distinct entities in WHO-HAEM4R, are retained in WHO-HAEM5. **Paediatric nodal marginal zone lymphoma** (pNMZL) is upgraded from a subtype under nodal marginal zone lymphoma to a separate entity. Although it shows overlapping features with paediatric-type follicular lymphoma, current published evidence is considered insufficient to group these two indolent paediatric diseases into one family at this time. **Primary cutaneous marginal zone lymphoma (PCMZL)** has also been designated as a separate entity in WHO-HAEM5, owing to its distinctive clinicopathologic features.

EMZL, NMZL, and PCMZL have overlapping histologic and immunophenotypic features: the neoplastic cells are mature small B cells typically negative for CD5 and CD10. Plasmacytic differentiation is common, and associated reactive lymphoid follicles are often present. However, despite some shared features, they have different etiologies and pathogenesis, with further differences among EMZLs arising in different anatomic sites. Trisomy of chromosomes 3 and 18 are common in all. Gains of chromosomes 2p and 6p, and loss of 1p and 6q are frequent in NMZL [71–77]; however, gain of 6p and loss of 6q are recurrently seen only in EMZL of the ocular adnexa [78]. Translocations involving *MALT1* such as t(11;18)(q21;q21), resulting in *BIRC3*::*MALT1* fusion, are recurrent in gastric and pulmonary EMZL but rare at other sites [79–83]. In contrast, no recurrent gene fusions or rearrangements are described in PCMZL or NMZL.

The mutational profiles of EMZL and NMZL differ [76, 84–86]. In addition, there are significant genetic differences among EMZLs arising in different anatomic sites (Fig. 2): e.g., ocular adnexal EMZL commonly shows *TNFAIP3* mutation/deletion [87, 88]; salivary gland EMZL shows recurrently mutated *GPR34* [89, 90]; most thyroid EMZL carry deleterious mutations of *CD274*, *TNFRSF14* and/or *TET2* [91]; and PCMZL often shows *FAS* mutations [92]. Somatic variants of *KMT2D*, *PTPRD*, *NOTCH2, KLF2*, and others are frequent in NMZL [76, 84, 85, 93] but not in EMZL. Better definition of the underlying molecular genetic changes of these lymphomas may potentially open the door to improved treatment options.

Follicular lymphoma (FL): from classic grading to biological grouping

The family of follicular lymphoma encompasses follicular lymphoma, in situ follicular B-cell neoplasm (ISFN), paediatric-type FL and duodenal-type FL. There are no significant updates on the latter three entities in WHO-HAEM5. In contrast, the entity of **follicular lymphoma** has undergone significant revision. The vast majority of FL (85%) have at least in part a follicular growth pattern, are composed of centrocytes and centroblasts and harbour the t(14;18)(q32;q21) translocation associated with *IGH*::*BCL2* fusion; these are now termed **classic FL (cFL)** and set apart from two related subtypes/groups, **follicular large B-cell lymphoma (FLBL)** and **FL with uncommon features (uFL)**.

In WHO-HAEM5, grading of FL, which is only pertinent to cFL, is no longer mandatory. This decision was made after extensive

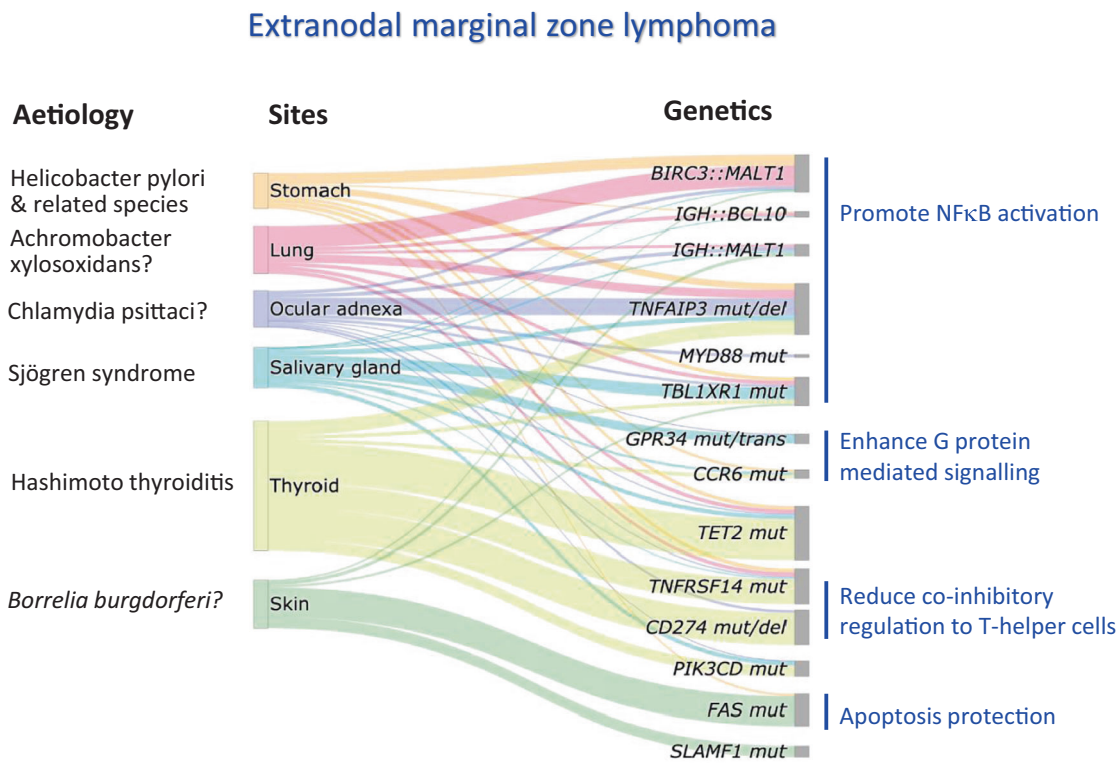

Fig. 2 Aetiology and recurrent genetic abnormalities in extranodal marginal zone lymphoma (EMZL) of various sites. An important clinical application is that *BIRC3*::*MALT1* identifies those cases of the gastric EMZL not responding to *H. pylori* eradication. As many of the genes involved in EMZL have not been uniformly investigated across different sites, only the recurrent genetic changes fundamental to the understanding of EMZL pathogenesis are presented. The height of the boxes under sites does not reflect the frequencies of these lymphomas. trans translocation, mut mutation, del: deletion.

discussions and evaluation of the literature centering on the reproducibility of grading and on its questionable clinical significance for individual patients in the era of modern therapy. Poor reproducibility may result from various causes, including sampling (complete lymph node excision versus core needle biopsy), definition and recognition of centroblasts, and methods of enumeration. Since grading of FL is based on the enumeration of centroblasts per high-power field (HPF), one of the challenges is the lack of a consistent definition of a HPF using a 40x microscope objective (400x magnification), where the size of the microscopic field has changed over the years even at the same magnification [94]. Lack of consensus regarding the morphological spectrum of centroblasts and using conventional methods of counting further negatively impacts reproducibility [95]. Clinical outcomes among patients with FL of grades 1, 2, and 3A seem not to be significantly different. Currently, patients are treated with similar protocols both in and outside clinical trials in many parts of the world [96–99]. While attempts have been made to improve reproducibility through digital applications or by using immunohistochemical supportive data, such methods have not been compared to patient outcome. Hence, it was deemed premature to include them in WHO-HAEM5 [100–102]. Taken together, for histopathologic as well as clinical reasons, it was felt timely to make grading of FL to be optional in the subtyping of cFL.

Rare cases of cFL grade 3A may show a focal or extensive diffuse growth pattern. In WHO-HAEM4R, the recommended diagnosis in such cases was "DLBCL with follicular lymphoma", even though sheets of large cells are not often present. Currently, it is uncertain whether such cases should better be classified as cFL or DLBCL [103] and therefore, treatment decisions in individual patients should not be based on pathology information alone but rather be made in multidisciplinary conference settings and await research to define more objective criteria to predict clinical course. The subtype of FLBL largely equals WHO-HAEM4R FL grade 3B, and renaming was done for reasons of consistency throughout the classification.

The newly introduced subtype of uFL includes two subsets that significantly diverge from cFL: one with "blastoid" or "large centrocyte" variant cytological features, and the other with a predominantly diffuse growth pattern [104, 105]. FL with "blastoid" or "large centrocyte" cytological features more frequently display variant immunophenotypic and genotypic characteristics and may show inferior survival [106]. They need to be distinguished from large B-cell lymphoma with *IRF4* rearrangement [107]. FL with a predominantly diffuse growth pattern frequently occurs as a large tumour in the inguinal region and is associated with CD23 expression, an absence of *IGH*::*BCL2* fusion [108], and frequent *STAT6* mutations along with 1p36 deletion or *TNFRSF14* mutation [104, 109]. Separating such cases from cFL will support research to clarify disease biology, allowing a better definition in future classifications.

Mantle cell lymphoma: Improved risk stratification

WHO-HAEM5 groups mantle cell neoplasia into three individual chapters. ***In situ* mantle cell neoplasm (ISMCN)** is rare and typically an incidental finding. It represents colonization of mantle zones of lymphoid follicles by B cells carrying an *IG*::*CCND1* fusion leading to cyclin D1 overexpression [110].

The *IGH*::*CCND1* fusion associated with t(11;14)(q13;q32) is the genetic hallmark of **mantle cell lymphoma (MCL)**, present in ≥95% of cases (i.e., cyclin D1-positive MCL subtype) [111, 112]. Occasionally, *IGK* or *IGL* serve as the *CCND1* translocation partner [113]. In the occasional cases of MCL that strongly express cyclin D1 protein but show no *CCND1* rearrangement by FISH, genomic studies have revealed cryptic rearrangements of *IGK* or *IGL* enhancers with *CCND1* [114–116]. In the small subset of MCL

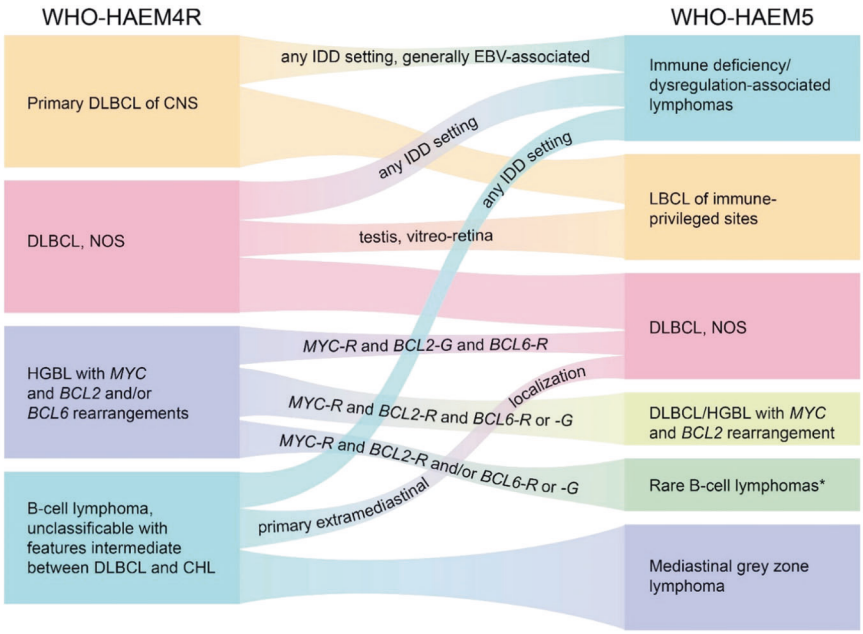

Fig. 3 Summary of the relationship between large B-cell lymphoma (LBCL) entities as named and defined in the revised 4th edition of the WHO classification (WHO-HAEM4R) and in the present 5th edition (WHO-HAEM5). * "Rare B-cell lymphomas" refer to those fulfilling definitions of specific clinico-pathological entities while incidentally bearing concomitant *MYC* and *BCL2* rearrangements. Examples are fluid-overload-associated large B-cell lymphomas and rare follicular lymphomas. R rearrangement, G germline configuration.

negative for cyclin D1 expression and *CCND1* rearrangement (i.e., cyclin D1-negative MCL subtype), *CCND2, CCND3*, or *CCNE* rearrangements have been identified as alternative mechanisms of cell cycle dysregulation [117]. In recent years, the median overall survival of patients with MCL has dramatically increased due to improved therapies. Hence, the identification of prognostic subgroups has become highly relevant. Widely available and best-established biomarkers of high-risk MCL include cytomorphology (pleomorphic or blastoid appearance), high Ki67 proliferative index, p53 expression and *TP53* mutation [118, 119].

Non-nodal MCL (nnMCL) is characterized by involvement of blood, bone marrow and spleen, little or no lymphadenopathy, a mostly asymptomatic presentation, and a better clinical outcome compared to MCL. Biologically, nnMCL differs from MCL by: (i) lack of SOX11 expression [120, 121], low Ki67 index and frequent lack of CD5 expression [122]; (ii) differences in the usage of *IGHV* gene segments with biased usage of the *IGHV1-8* gene [122] together with a higher somatic hypermutation load [121, 123, 124]; and (iii) fewer genetic alterations and infrequent genomic complexity [120, 125].

High-grade transformation steps forth

For the first time, WHO-HAEM5 now includes a section with the description of **High-grade transformation of indolent B- cell lymphomas** including a summary of the incidence of known and driver genes.

Large B-cell lymphomas: new names and new umbrellas

The family of **large B-cell lymphomas** comprises a wide spectrum of tumours. Although these are generally composed of medium-sized to large cells with round to ovoid nuclei and vesicular chromatin, cases with intermediate-sized and blastoid cells may also meet criteria for this family. These require delineation from morphologically similar entities, such as the blastoid variant of mantle cell lymphoma and lymphoblastic leukaemia/lymphoma.

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) represents the most common entity, and is defined by large-cell morphology as above, mature B-cell phenotype, and lack of criteria defining specific large B-cell lymphoma entities. The lymphomas encompassed within DLBCL, NOS are morphologically and molecularly heterogeneous. Since most DLBCL, NOS broadly recapitulate the differentiation and maturation mechanisms active in germinal centers (GC), two main subtypes previously defined in WHO-HAEM4R continue to be recognized. The germinal centre B-cell-like (GCB) subtype has a gene expression profile (GEP) related to a GC cell of origin (COO), and is enriched for *IGH::BCL2* fusion due to t(14;18)(q32;q21) and mutations of genes instrumental for GC development, GC dark zone and light zone transitions and microenvironmental interactions, such as *EZH2, GNA13, MEF2B, KMT2D, TNFRSF14, B2M* and *CREBBP* [126]. The activated B-cell-like (ABC) subtype derives from cells of GC exit or post GC origin, with either germinal center-exit or early plasmablastic phenotype. It is characterized by dependence on BCR signaling and NFκB activities, is negative for most GC markers, and expresses IRF4/MUM1 [127]. It is enriched for BCR pathway mutations such as in *MYD88* (mostly p.L265P), *CD79B* and *PIM1*, as well as genetic changes that block the B-cell differentiation program such as *BCL6* rearrangements and *PRDM1/BLIMP1* mutation/deletion [126]. It is recommended to continue rendering the GCB/ABC (GCB/nonGCB) distinction although it has become apparent that the clinical impact of COO stratification is relatively limited outside clinical trials. Although IHC algorithms obviously do not recognize the "unclassified" GEP category and have concordance issues with GEP, they are widely used in routine practice. Recent data from next generation sequencing studies have illustrated a heterogeneous molecular landscape of DLBCL, NOS with around 150 genetic drivers that are recurrently mutated in DLBCL, with a mean of approximately 8% of these genes mutated per patient [128]. Interestingly, in spite of the use of various sequencing approaches and clustering algorithms, the genetic landscape of DLBCL, NOS can be used for sub-classification with broad concordance suggesting that the underlying disease biology can be captured by mutational analysis. Some of the genetic groups harbour a mutational profile that in part overlaps with those of FL or MZL, suggesting either transformation from these low-grade lymphomas or a common path in their early pathogenesis. However, no unifying concept for proposed clusters and the significance of their genetic drivers has been established so far,

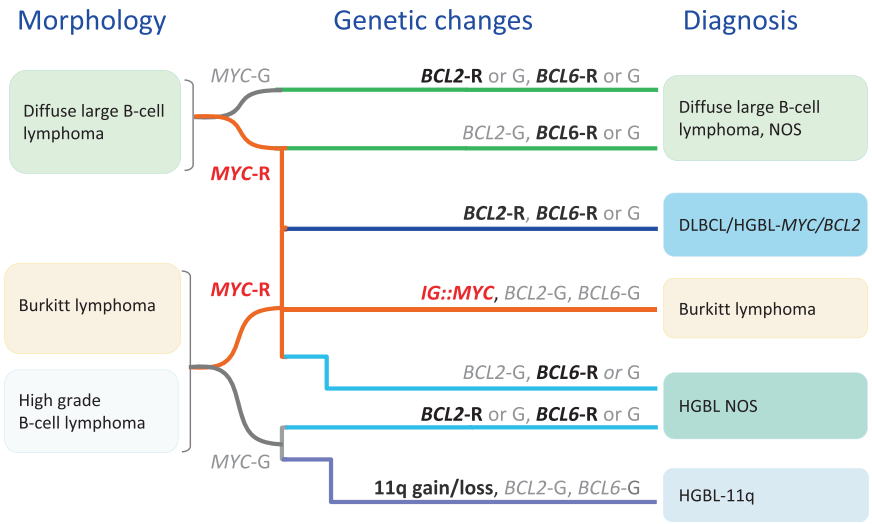

Fig. 4 Algorithm for classification of aggressive B-cell lymphomas in WHO-HAEM5 in the light of *MYC*, *BCL2* and *BCL6* rearrangement and complex 11q gain/loss patterns. HGBL high grade B-cell lymphoma, R rearrangement, G germline configuration.

precluding the definition of a unified genetic framework of DLBCL, NOS at the present time. Moreover, the impact of these genetic clusters on outcome and as a basis for targeted treatment approaches is currently unclear and awaits evidence from clinical trials. Therefore, it was considered premature to introduce such molecular classifications in WHO-HAEM5.

WHO-HAEM5 recognizes 17 specific entities as "large B-cell lymphomas" other than DLBCL, NOS (Table 1 and Fig. 3**)**. For most of these entities, biological concepts and diagnostic strategies have remained largely unchanged compared with WHO-HAEM4R. However, the names of some entities have been modified for reasons of consistency, from "diffuse large B-cell lymphoma" to "large B-cell lymphoma", acknowledging the fact that a diffuse growth pattern is either not apparent/present or cannot be assessed in some entities (e.g., fibrin-associated large B-cell lymphoma or fluid-overload associated large B-cell lymphoma).

The WHO-HAEM4R entity of high-grade B-cell lymphoma with dual rearrangements of *MYC* and *BCL2* and/or *BCL6* has been conceptually reframed and reassigned. In recognition of their variable morphologies but homogeneous dark zone biologic features and gene expression characteristics, the WHO-HAEM5 renames the entity **diffuse large B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements** (DLBCL/HGBL-*MYC/BCL2*) to encompass tumours defined by the presence of dual *MYC* and *BCL2* rearrangements that may be composed of large or intermediate or blastoid cells (Fig. 4). Hence, the primary morphological categorization of the neoplasm can be maintained after determining the genetic constitution. This group of cases forms a homogeneous entity with an exclusive GC gene expression profile, a close pathogenetic relationship to FL and molecular GC-like DLBCL subsets [129–132]. In addition, gene expression signatures associated with DLBCL/HGBL-*MYC/BCL2 (MHG, DHITsig)* [130, 133] significantly overlap with those of Burkitt lymphoma (BL). In contrast, lymphoid neoplasms with dual *MYC* and *BCL6* rearrangements represent a more diverse spectrum [129] with variable gene expression profiles and mutational spectra, markedly differing from DLBCL/HGBL-*MYC/BCL2*. Hence, these cases have been excluded from the DLBCL/HGBL-*MYC/BCL2* entity and are now classified either as a subtype of DLBCL, NOS or HGBL, NOS according to their cytomorphological features (Fig. 4).

High-grade B-cell lymphoma with 11q aberration (HGBL-11q), formerly known as Burkitt-like lymphoma with 11q aberration in WHO-HAEM4R, is an aggressive *MYC* rearrangement-negative mature B-cell lymphoma with a morphology similar to Burkitt lymphoma (BL) or with an intermediate or blastoid appearance, an immunophenotype (CD10+, BCL6+, BCL2-), and/or gene expression profile (GEP) similar to BL, and a characteristic chromosome 11q-gain/loss pattern. The losses in 11q24qter are more specific to this entity than the centromeric gains but rarely might be substituted by copy-number neutral losses of heterozygosity. More recent studies have also confirmed that the mutational spectrum, besides the pattern of genomic imbalances, is different from that of BL and is more similar to that of DLBCL of GCB type. Of note, genomic alterations affecting the ID3-TCF3 complex, one of the molecular hallmarks of BL, are only rarely, if at all, seen in HGBL-11q [134, 135]. Cases of B-cell lymphoma with a Burkitt-like appearance that lack *MYC* rearrangement, therefore, should be tested for the 11q gain/loss pattern [136] (Fig. 4). It should be noted that the morphological spectrum of HGBL-11q as defined by the specific 11q-gain/loss pattern is more restricted than that of DLBCL/HGBL-*MYC/BCL2*.

Large B-cell lymphomas (LBCL) of immune-privileged sites is a new umbrella term introduced in WHO-HAEM5 to acknowledge common biological features of a group of aggressive B-cell lymphomas that arise as primary tumours in the central nervous system (CNS), the vitreoretinal compartment, and the testes of immunocompetent patients. This new entity now combines the previous entity of primary DLBCL of CNS with DLBCL of the vitreoretina and testis that were previously included among DLBCL, NOS. They arise in immune sanctuaries created by their respective anatomical structures (e.g., the blood-brain, blood-retinal, and blood-testicular barriers), and immune regulation systems within their respective primary sites, and share immunophenotypic and molecular features [137–139] (Table 4). Information on this group of tumours is rapidly accruing: it appears that some lymphomas arising at other distinct sites such as the breast and skin share some of these features, and thus, this group of 'immune-privileged lymphomas' might expand in future classifications.

Fluid overload-associated large B-cell lymphoma is a new addition to the list of large B-cell lymphomas in WHO-HAEM5, being distinct from primary effusion lymphoma (PEL). This entity has been briefly alluded to in the 5th Edition of the WHO Classification of Thoracic Tumours, under the names "PEL-like lymphoma" or "HHV8-unrelated PEL-like lymphoma" [140]. Patients usually are adults, predominantly elderly, without underlying immunodeficiency, who present with exclusive involvement of body cavities, most commonly the pleural cavity [141–143]. They frequently have an underlying condition causing fluid overload, such as chronic heart failure, renal failure, protein-

Table 4. Distinctive features of primary large B-cell lymphomas of immune privileged sites.

Subtypes	Primary large B-cell lymphoma of the CNS
	Primary large B-cell lymphoma of the vitreoretina
	Primary large B-cell lymphoma of the testis
Clinical	Usually in adults over age of 60 years
	Lymphoma tends to "home" to other immune privileged sites: vitreoretina tumour may occur concurrently with or follow CNS tumour; testicular tumour tends to relapse in CNS or contralateral testis
	Aggressive tumours with generally poor prognosis
Morphology	Large B-cell lymphoma
Immunophenotype	Activated B-cell immunophenotype: Usually CD10-, MUM1+, BCL6+
	EBV negative
Mutational profile	Concomitant *MYD88* and *CD79B* mutations
	Immune evasion: genetic inactivation of MHC class I and II and *B2M* (β_2-microglobulin) with subsequent loss of protein expression
	Showing DLBCL genomic signature C5/MCD/MYD88

losing enteropathy or liver failure/cirrhosis. The neoplastic large cells exhibit a mature B-cell rather than plasmablastic immunophenotype. KSHV/HHV8 is negative, while EBV is positive in 13–30% of cases and the genomic landscape differs essentially from primary effusion lymphoma (PEL) [141, 142]. The prognosis appears to be fairly favorable, yet another reason for distinction from PEL.

Mediastinal gray zone lymphoma (MGZL) is a B-cell lymphoma with overlapping features between primary mediastinal B-cell lymphoma (PMBL) and classic Hodgkin lymphoma (CHL), especially nodular sclerosis CHL (NSCHL). This entity replaces the term "B-cell-lymphoma, unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma" of the WHO-HAEM4R, taking into account that lymphomas with these features are specific to the mediastinum and are part of a single biologic group with a morphologic and immunophenotypic spectrum from CHL to PMBL, with MGZL straddling the two. Current evidence indicates that cases with morphologic and immunophenotypic features similar to MGZL, but occurring outside and without involvement of the mediastinum, harbour different gene expression profiles and DNA alterations [143]. Hence, these cases are better classified as DLBCL, NOS.

High grade B-cell lymphoma, NOS (HGBL, NOS) represents aggressive mature B-cell lymphomas composed of medium-sized or blastoid cells that do not fit into other well-defined entities. NGS-based analyses of the mutational spectrum and gene expression signatures suggest that HGBL, NOS is a heterogeneous category, also including activated B-cell lymphomas with mutations of *MYD88, CD79B*, or *TBL1XR1*. Most frequent mutations are found in *KMT2D* (43%) and *TP53* (30%). By GEP, most cases of HGBL, NOS have been reported to group into the "unclassified" cluster, and the remainder are variably classified in the other clusters [144]. Interestingly, gene expression profiling showed that 54% of HGBL, NOS harbour the "double hit" signature (DHITsig) characteristic of LBCL/HGBL with *MYC/BCL2* despite lacking rearrangements of these genes [144].

Burkitt lymphoma: EBV matters

The definition of **Burkitt lymphoma (BL)** in WHO-HAEM5 remains largely unchanged, describing BL as an aggressive mature B-cell neoplasm composed of medium-sized cells with a germinal center B-cell phenotype CD10+, BCL6+, BCL2-/weak, high Ki67 index (>95%) and an *IG::MYC* juxtaposition (Fig. 4). Whereas three subtypes of BL have been historically recognized ("endemic", "non-endemic or sporadic", and "immunodeficiency-associated") [145], more recent data suggest that EBV-positive BL and EBV-negative BL form discrete biologic groups based on their molecular features regardless of epidemiologic context and geographic location and therefore supersede the epidemiological subtyping [146–151]. EBV infection plays an essential role early in pathogenesis causing B cells to evade apoptosis [152, 153]. Emerging evidence suggests a dual mechanism of BL pathogenesis: virus-driven versus mutational, depending on EBV status [147]. EBV-positive and EBV-negative BL share evidence of coding mutations affecting pathways such as BCR and PI3K signaling, apoptosis, SWI/SNF complex and GPCR signaling [149, 154, 155]. In comparison with EBV-negative BL, EBV-positive BL shows significantly higher levels of somatic hypermutation particularly in noncoding sequences close to the transcription start site [149], harbours fewer driver mutations, particularly in the apoptosis pathway [149], and shows a lower frequency of mutations in the genes encoding the transcription factor TCF3 or its repressor ID3 [149]. To acknowledge these recent insights into BL biology, the distinction of the two subtypes, EBV-positive BL vs. EBV-negative BL, is recommended by WHO-HAEM5.

KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas

WHO-HAEM5 recognizes the full spectrum of lymphoid proliferations related to Kaposi sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8) infection, which in parallel with the terminology for other herpesviruses is now indicated as KSHV/HHV8 to accommodate both the common practices of haematopathologists and of virologists. These lymphoid proliferations include **KSHV/HHV8-associated multicentric Castleman disease (KSHV/HHV8-MCD)** [covered under the category "Tumour-like lesions with B-cell predominance"], **germinotropic lymphoproliferative disorder (KSHV/HHV8-GLPD)**, **primary effusion lymphoma (PEL)**, **extracavitary PEL (EC-PEL)** and **KSHV/HHV8-positive diffuse large B-cell lymphoma (KSHV/HHV8-DLBCL)** [156, 157]. PEL/EC-PEL and KSHV/HHV8-DLBCL are characteristically seen in HIV patients, but can be seen in other immunodeficiency settings. KSHV/HHV8-GLPD, in contrast, is more prevalent in elderly patients without overt immunodeficiency, although it has also been reported in HIV-positive individuals. In addition, KSHV/HHV8-MCD is seen in both HIV-positive and HIV-negative patients, but the latter are overall older [158–160]. The diagnosis of prototypical examples of the various KSHV/HHV8-associated entities is often straightforward based on the definitions as formulated in WHO-HAEM5. It has become clear, however, that the morphological and clinical spectrum of KSHV/HHV8-associated entities is broader than previously appreciated [161]. Moreover, there are individual patients in whom clinical, histologic and viral features (KSHV/HHV8 with or without EBV) overlap among entities. Observations of synchronous and metachronous presentation of

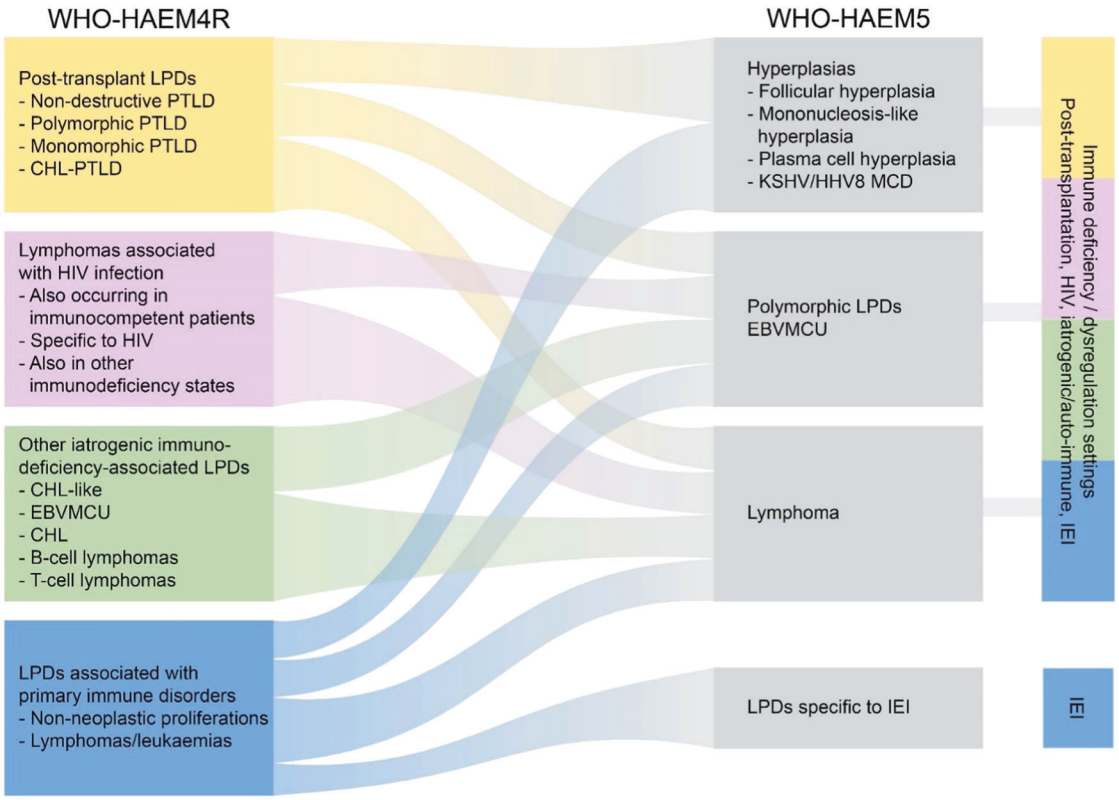

Fig. 5 Summary of the relationship between immunodeficiency-associated lymphoid proliferations and lymphomas as named and defined in the revised 4th edition of the WHO Classification (WHO-HAEM4R) and in the present 5th edition (WHO-HAEM5). The overarching concept applied in WHO-HAEM5 recognizes the pathological and biological similarities between proliferations presenting in various immune deficiency settings, while acknowledging their specific features. Outside the shared entities, unique proliferations are especially typical for various inborn errors of immunity (IEI). EBVMCU: EBV-positive mucocutaneous ulcer.

Table 5. Three-part nomenclature for lymphoid proliferations and lymphomas arising in the setting of immune deficiency/dysregulation.

Histological diagnosis	Viral association	Immune deficiency/dysregulation setting
◦ Hyperplasia (specify type) ◦ Polymorphic lymphoproliferative disorder ◦ Mucocutaneous ulcer ◦ Lymphoma (classify as for immunocompetent patients)	◦ EBV +/− ◦ KSHV/HHV8 +/−	◦ Inborn error of immunity (specify type) ◦ HIV infection ◦ Posttransplant (specify: solid organ/bone marrow) ◦ Autoimmune disease ◦ Iatrogenic/therapy-related (specify) ◦ Immune senescence

different KSHV/HHV8-associated lesions, and cases that possess morphological and/or clinical features of more than one entity support the notion that these equivocal cases may result from the special biology of KSHV/HHV8, which is not adequately captured by current disease-defining criteria [158, 161, 162]. For example, distinction between lymph node-based extracavitary PEL and KSHV/HHV8-positive DLBCL is difficult and may be arbitrary. WHO-HAEM5 acknowledges the limitations of its definitions. While more data to support biology-defined boundaries among the entities are awaited, it is recommended that decisions on classification and optimal therapy should be resolved in a multidisciplinary setting in challenging cases.

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation: a new approach to order patterns

WHO-HAEM5 has introduced major changes to the classification of immunodeficiency-associated lymphoproliferative disorders (Fig. 5). In prior classifications, these disorders were grouped according to the disease background in which they arose and were discussed in separate chapters: primary immunodeficiencies, HIV infection, post-transplantation and other iatrogenic immunodeficiencies. This approach has been valuable for many years in supporting clinical decision-making and as a basis for translational and basic research. Knowledge that has resulted from this approach supports the notion that morphological features and, to a certain extent, the biology of many of these entities overlap and that the spectrum of immunodeficiency settings is broader than previously recognized. Therefore, it was considered timely to introduce an overarching framework and a standardized nomenclature to cover the different settings of immune dysfunction, according to the unifying nomenclature proposed at the Workshop on Immunodeficiency and Dysregulation organized by the Society of Hematopathology and European Association for Haematopathology in 2015 [163]. This framework aims to focus attention on shared histologic and pathogenetic features as well as to accommodate distinct causal associations of specific lesions and specific clinical and/or therapeutic consequences [163, 164]

Table 6. Immuno-morphological growth patterns of NLPHL.

Designation	Description
Pattern A	Classic B-cell nodular
Pattern B	Serpiginous/interconnected
Pattern C	Prominent extra-nodular LP cells
Pattern D	T-cell-rich nodular
Pattern E	Diffuse THRLBCL/DLBCL-like
Pattern F	Diffuse moth-eaten, B-cell-rich

THRLBCL T-cell/histiocyte-rich large B-cell lymphoma.

The new standardized nomenclature builds on an integrated approach to diagnosis that combines all relevant data into a reporting system as follows (Table 5):

1) Histological diagnosis according to accepted criteria and terminology;
2) Presence or absence of one or more oncogenic virus(es); and
3) The clinical setting/immunodeficiency background.

This nomenclature addresses existing inconsistencies in terminology and diagnostic criteria for similar lesions in different immunodeficiency settings, may improve communication among multidisciplinary teams in guiding appropriate clinical management as well as research studies, and facilitate incorporation of emerging knowledge in the field. As the same pathological entity, e.g., polymorphic lymphoproliferative disorder, does not necessarily have the same pathogenesis or clinical behaviour in different immune deficiency/dysregulation settings, this underscores the need to include the immune deficiency/dysregulation setting as a required part of the three-part nomenclature.

New types of immunodeficiency settings continue to be recognized [165–167]. Poly-chemotherapy for treatment of solid tumours and haematologic neoplasms has been largely accepted as an underlying cause for immunodeficiency. However, it is as yet unclear which polychemotherapy regimens confer this risk, and how long the risk persists [168]. In addition, with increasing use of novel immune modulatory agents, unanticipated types of immune dysfunction are emerging, e.g., in the aftermath of CAR-T cell and/or checkpoint inhibition therapies. Immune senescence is another setting that is poorly understood and as yet not possible to define or exclude; thereby use of an arbitrary age as cut-off does not have a scientific basis [169]. All these emerging concepts call into question the adequacy of the term "immunodeficiency", which does not capture the extent, depth or phenotypic variation of immune suppression and the milieu of deregulated immune cell subsets. Therefore, WHO-HAEM5 has adopted "immune deficiency/dysregulation" (IDD) as the preferred term to encompass this expanding disease spectrum.

Primary immunodeficiencies, associated with germline mutations, have been renamed "inborn errors of immunity" (IEI) by the International Union of Immunological Societies, a terminology adopted by WHO-HAEM5 [170]. Patients with IEI may develop distinctive types of lymphoid proliferations unique to the particular IEI, as well as those described in the acquired IDD settings. The types and frequency of these proliferations are largely dependent on the immune dysregulation conferred by the germline aberration underlying a respective IEI. Given the overlap with other IDD settings, IEI-associated lymphoid proliferations and lymphomas have been incorporated into the overarching framework and nomenclature of "lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation."

The new approach to the classification of IDD-associated lymphoid proliferations and lymphomas impacts other lymphoid entities that are described in separate WHO chapters. This especially holds true for diagnoses in which EBV plays a defining or important role, including EBV-positive DLBCL, lymphomatoid granulomatosis, and CHL. In WHO-HAEM5, harmonization of diagnostic criteria among these categories has been undertaken as much as currently feasible, while at the same time acknowledging that some terminologies are arbitrary. For example, should an elderly patient with a DLBCL harbouring EBV be diagnosed as having EBV+ DLBCL or DLBCL, EBV+, in an IDD setting based upon presumed immune senescence? Clarification of these disease boundaries awaits further clinico-pathological data and further insights into disease pathogenesis, which will allow evidence-based refinements to the classification.

Hodgkin lymphoma: CHL clearly defined from its mimickers, NLPHL on the way to, but not yet NLPBCL

Classic Hodgkin lymphoma (CHL) comprises a group of B-cell neoplasms derived from germinal center B-cells, characterized by a low number of tumour cells embedded in a reactive microenvironment rich in immune cells. The large diagnostic Hodgkin and Reed-Sternberg (HRS) cells characteristically show a defective B-cell program. The defining immunophenotype of HRS cells remains unchanged from WHO-HAEM4R, as are criteria for nodular sclerosis (NSCHL), mixed cellularity (MCCHL), lymphocyte rich (LRCHL), and lymphocyte depleted (LDCHL) subtypes. With modern treatment protocols, these subtypes have lost most of their prognostic relevance. However, there is still merit in describing these subtypes to support epidemiological and translational studies, since specific subtypes are associated with different clinical features and underlying biologies [171]. While the basic description has not changed substantially since the last century, WHO-HAEM5 includes a comprehensive section on the etiology and pathogenesis of CHL, in particular incorporating new data on the crucial role of the microenvironment in modulating the disease [172, 173]. Recent biological insights have led to the recognition of an expanding spectrum of pitfalls, grey zones and mimickers, among them nodal T follicular helper cell lymphomas and lymphoproliferative disorders arising in immune deficiency/dysregulation settings that may contain EBV-positive HRS-like cells [163, 174, 175]. Caution should be exercised, therefore, when considering the diagnosis of CHL in the IDD setting; the same applies to purely extranodal CHL-like lymphoproliferations.

WHO-HAEM5 continues to list **nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)** under the family of Hodgkin lymphoma; the existing terminology of NLPHL (Hodgkin lymphoma) is maintained so as not to interfere with ongoing clinical trials. However, NLPHL may be more accurately called "nodular lymphocyte predominant B-cell lymphoma" since the neoplastic cells have a functional B-cell program, and therefore this term is now considered acceptable in preparation of future definitive adoption of the new nomenclature. An important issue in NLPHL is the recognition of the different growth patterns [176] overlapping with T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) at the extreme end (Table 6) [177]. These patterns occur across all age groups. Some variant patterns (patterns C, D and E) have been associated with more aggressive clinical behaviour in retrospective analyses [177–179] and may thus reflect the natural development and progression of the tumour [180, 181]. In some cases, a clear distinction between NLPHL Pattern E and THRLBCL may not be possible since both diseases present with advanced clinical stage. Distinction is especially difficult on small biopsies, which may not be representative.

Plasma cell neoplasms and other diseases with paraproteins: new conditions from AESOP to TEMPI

The section on plasma cell neoplasms in WHO-HAEM5 recognizes new entities and incorporates structural modifications as a step forward from WHO HAEM4R. New conditions included are **monoclonal gammopathy of renal significance (MGRS)**, **cold agglutinin disease (CAD)**, as well as **TEMPI syndrome**

(a provisional entity in WHO-HAEM4R, characterized by telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting) and **AESOP syndrome** (adenopathy and extensive skin patch overlying a plasmacytoma). Sections based on types of paraproteins and disease burden have been reorganised. CAD, IgM and non-IgM MGUS and MGRS are grouped as monoclonal gammopathies, and diseases with abnormal monoclonal immunoglobulin deposits are grouped together. The heavy chain diseases (HCD) are now included in the plasma cell neoplasms section.

Cold agglutinin disease (CAD) is an autoimmune haemolytic anemia mediated by monoclonal cold agglutinins and driven by an underlying clonal B-cell lymphoid proliferation not fulfilling criteria for a B-cell lymphoma. The annual incidence of this rare disease is estimated at 1–1.8 per million; its prevalence is four-fold higher in colder countries [182–184]. **Monoclonal gammopathy of renal significance (MGRS)** represents a plasma cell or B-cell proliferation that does not meet accepted criteria for malignancy but secretes a monoclonal immunoglobulin or immunoglobulin fragment resulting in kidney injury [185, 186]. About 1.5% of patients whose disease would otherwise be classified as MGUS have MGRS [187].

The risk stratification model for **IgM MGUS** and **non-IgM MGUS** has been updated. Presence of all 3 risk factors consisting of: (1) an abnormal serum free light chain ratio, (2) IgA or IgM type MGUS, and (3) serum M-protein value >1.5 g/dL is considered high risk with approximately 50–60% risk of progression at 20 years, whereas the risk is only 5% when none of the risk factors are present [188]. A diagnosis of **TEMPI syndrome** is primarily made on clinical and imaging investigations. The bone marrow is unremarkable in the majority of cases; a few cases show erythroid hyperplasia and a low-volume of light chain-restricted plasma cells [189, 190]. Skin biopsies of patients with **AESOP syndrome** show diffuse hyperplasia of dermal vessels associated with surrounding dermal mucin, and lymph nodes can show features mimicking Castleman disease [191, 192].

New data have emerged concerning the progression from precursor states to **plasma cell (multiple) myeloma (PCM)**, involving branching evolutionary patterns, novel mutations, biallelic hits in tumour suppressor genes, and segmental copy number changes [193]. While 1q21 gain is often an early event, translocations and additional amplifications of 1q21 emerge later during pathogenesis [194]. Staging of PCM according to the Revised International Staging System for Multiple Myeloma proposed by the International Myeloma Working Group has been adopted [195]. The important role of minimal/measurable residual disease (MRD) using next-generation flow cytometry or next-generation sequencing of immunoglobulin gene rearrangements as well as PET/CT in assessing prognosis and risk stratification in patients with PCM has been detailed [196, 197].

T-cell and NK-cell lymphoid proliferations and lymphomas

WHO-HAEM5 has reorganized entities that were listed as mature T- and NK-cell neoplasms in WHO HAEM4R to include a broader group of entities under the heading of "T-cell and NK-cell lymphoid proliferations and lymphomas" (Table 2). Notably, included is a family/class of tumour-like lesions with T cell predominance. Precursor T-lymphoblastic neoplasms are also included under this overarching category as a separate family. The mature T-cell and NK-cell neoplasms are grouped into 9 families based on diverse concepts: cell of origin/differentiation state, clinical scenario, disease localization, and cytomorphology. While most T- or NK-cell neoplasms can be assigned to the respective T- or NK-cell lineage, they are not separated as two categories in WHO-HAEM5 because some entities comprise a spectrum of tumours of NK, T, hybrid or indeterminate phenotype, such as in extranodal NK/T-cell lymphoma, EBV+ nodal T- and NK-cell lymphoma, chronic active EBV disease and severe mosquito bite allergy. In other instances, distinction between T- and NK-cell origin may be unclear or difficult to determine.

Tumour-like lesions with T-cell predominance: a new class of tumour-like lesions

The new family of **tumour-like lesions with T-cell predominance** in WHO-HAEM5 includes three distinct entities: indolent T-lymphoblastic proliferation (ITLP), Kikuchi-Fujimoto disease (KFD), and autoimmune lymphoproliferative syndrome (ALPS). These expansions of T cells can potentially be mistaken for lymphoma. **Indolent T-lymphoblastic proliferation (ITLP)** may occur by itself or in association with benign and neoplastic follicular dendritic cell proliferations and other malignancies. It shows clusters or confluent sheets of lymphoid cells which can range in appearance from small lymphocytes to slightly larger cells with more open chromatin (morphologically consistent with thymocytes as seen in the normal thymus), which may be mistaken for T-lymphoblastic leukaemia/lymphoma due to TdT expression [198–205]. However, ITLP may distort, but typically does not obliterate the architecture of the involved tissues, the TdT+ cells are not as atypical as those encountered in lymphoblastic leukaemia/lymphoma, and ITLP does not show monoclonal TCR gene rearrangement. **Kikuchi-Fujimoto disease (KFD)** commonly shows large aggregates and sheets of T immunoblasts and histiocytes, accompanied by prominent apoptosis in lymph nodes, mimicking peripheral T-cell lymphoma NOS. Clues to the correct diagnosis include the typical clinical scenario of cervical lymphadenopathy in a young woman, the circumscribed and non-expansile nature of the nodal infiltrate, presence of a significant component of plasmacytoid dendritic cells (CD123+) and presence of many histiocytes that express myeloperoxidase. **Autoimmune lymphoproliferative syndrome (ALPS)**, which is associated with autoimmunity and germline or somatic pathogenetic changes in genes involved in FAS-mediated apoptosis [206], has nodal or extranodal infiltrates of CD4-, CD8- T cells, which may appear as atypical medium-sized cells with clear cytoplasm that may mimic lymphoma. The clinical setting (young patient age) and lack of destructive infiltrate may provide clues to its benign nature [207].

Precursor T-cell neoplasms: uncertainties about NK-lymphoblastic leukaemia/lymphoma

T-lymphoblastic leukaemia/lymphoma (T-ALL) are precursor T-cell neoplasms, comprising T-lymphoblastic leukaemia/lymphoma NOS and early T-precursor lymphoblastic leukaemia/lymphoma, as in WHO-HAEM4R. The latter shows a gene expression signature corresponding to that of earlier stages of normal precursor T cells as compared with the former entity, and shows a unique immunophenotype that includes expression of stem cell and/or myeloid markers. Despite significant advances in our understanding of the genetic background of T-ALL [208], there is as yet not sufficient evidence to establish genetically defined types of T-ALL with clinical relevance.

NK-lymphoblastic leukaemia/lymphoma, considered a provisional entity in WHO-HAEM4R, is not separately listed in WHO-HAEM5 because of lack of clear-cut and reliable diagnostic criteria, lack of published information on expression on NK-cell-associated antigens such as CD94 and CD161, and marked morphologic and immunophenotypic overlap with other entities, such as blastic plasmacytoid dendritic cell neoplasm, CD56+ T-ALL, CD56+ acute myeloid leukaemia and CD56+ acute undifferentiated leukaemia [209].

Mature T-cell and NK-cell leukaemias: a family is growing

The family of **mature T-cell and NK-cell leukaemias** encompasses neoplastic T- and NK-cell proliferations that primarily present as leukaemic disease, including T-prolymphocytic leukaemia (T-PLL), T-large granular lymphocytic leukaemia (T-LGLL),

NK-large granular lymphocytic leukaemia (NK-LGLL), adult T-cell leukaemia/lymphoma (ATLL), Sezary syndrome (SS) and aggressive NK-cell leukaemia (ANKL). Enhanced molecular understanding is considered sufficiently mature to permit incorporation of such features in the diagnostic criteria or prognostic markers of these diseases, where relevant.

T-prolymphocytic leukaemia (T-PLL) is a rare form of mature T-cell leukaemia with a heterogeneous clinical course. Recent efforts to standardize diagnosis, staging and treatment response [210] have led to unified diagnostic criteria, which include T lymphocytosis (>5 x 10^9/L) with appropriate phenotype, T-cell monoclonality and the presence of genetic aberrations including structural variants with breakpoints affecting the *TCL1A* or *MTCP1* locus or expression of TCL1. There is emerging evidence of clinical and phenotypic significance of specific mutations in **T-large granular lymphocytic leukaemia (T-LGLL).** *STAT3* mutation, found preferentially in CD8+ T-LGLL and gamma/delta T-LGLL, is associated with neutropenia and poorer overall survival [211–214]. *STAT5B* mutation is over-represented in the rare CD4+ T-LGLLs (present in up to 30% of cases); it is associated with a poor prognosis in CD8+ T-LGLL, but has no prognostic impact in CD4+ T-LGLL and gamma/delta T-LGLL [214]. "Chronic lymphoproliferative disorder of NK cells" in WHO-HAEM4R has been renamed **NK-large granular lymphocytic leukaemia (NK-LGLL)**, given recent evidence that this is a monoclonal or oligoclonal expansion of NK cells that has many similarities with T-LGLL. Genetic analyses of **adult T-cell leukaemia/lymphoma (ATLL)** have revealed novel events that highlight the importance of immune evasion including *CTLA4*::*CD28* and *ICOS*::*CD28* fusions, *REL* C-terminal truncations [215, 216], recurrent alterations in *HLA-A* and *HLA-B* and structural variations disrupting the 3′-untranslated region of *CD274* (*PD-L1)* [217]. Furthermore, the frequency and pattern of somatic alterations appear to be correlated with clinical behavior. Specifically, aggressive subtypes show more genetic alterations, whereas *STAT3* mutations are more common in indolent subtypes. Based on clinical and serological features, prognostic indices of ATLL have been better defined, and a prognostically meaningful genetic classification has recently been proposed [218]. **Sezary syndrome (SS)**, while closely related to mycosis fungoides but a distinct entity, is included in this section to highlight its primary site of clinical presentation and consideration in the differential diagnosis of mature T-cell leukaemias. Comprehensive analyses of genomic signatures [219] highlight the contribution of cellular aging and UV exposure observed in SS. Genome-wide sequencing studies have provided novel insights into pathogenetic events in **aggressive NK-cell leukaemia (ANKL)**. They implicate mutations in genes of the JAK/STAT and RAS/MAPK pathways, epigenetic modifiers (*TET2, CREBBP, KMT2D*), and immune checkpoint molecules *CD274* (*PD-L1*)/*PDCD1LG2 (PD-L2*) [220–223] in disease pathogenesis.

Primary cutaneous T-cell lymphoid proliferations and lymphomas (CTCL): rare subtypes become entities

Primary cutaneous T-cell lymphoid proliferations and lymphomas (CTCL) comprise a dedicated family within the mature T/NK-cell neoplasms chapter in WHO-HAEM5, and include nine entities.

In WHO-HAEM4R, primary cutaneous gamma/delta T-cell lymphoma, CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, acral CD8-positive T-cell lymphoproliferative disorder and CD4-positive small or medium T-cell lymphoproliferative disorder were grouped together under the term 'cutaneous peripheral T-cell lymphoma, rare subtypes', but are now each listed as separate entities in WHO-HAEM5 acknowledging their specific clinicopathological and genetic characteristics. The variants of mycosis fungoides from WHO-HAEM4R remain in place as subtypes; however, within the folliculotropic category, clinical early versus advanced stage patterns are described, and should be distinguished, to acknowledge differing clinical outcomes. There still remain rare cases that do not fit into the other known CTCL entities, and that are grouped into the newly coined entity "primary cutaneous peripheral T-cell lymphoma, NOS", awaiting further studies to clarify their nature [224].

As there is morphologic and immunophenotypic overlap among the various forms of primary CTCL, correlation with clinical history, signs and symptoms is a key element of the diagnostic work-up. Thus, dermatological examination and clinical photographic documentation are indispensable in reaching the correct diagnosis [224, 225].

Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas: indolent NK-cell lymphoproliferative disorder as the new kid in town

In WHO-HAEM5, the main changes in the classification of intestinal T-cell and NK-cell lymphomas include: new nomenclature for indolent T-cell lymphoproliferative disorder of the gastrointestinal tract, now designated "indolent T-cell lymphoma of the gastrointestinal (GI) tract", and addition of a new entity, "indolent NK-cell lymphoproliferative disorder of the GI tract" (iNKLPD) (Table 7). For **indolent T-cell lymphoma of the gastrointetinal (GI) tract**, the change from the conservative designation of "lymphoproliferative disorder" to "lymphoma" is justified by the significant morbidity related to the tumour and the ability of the disease to disseminate, while the qualifier "indolent" remains to indicate its protracted clinical course [226–230]. There are interesting correlations between T-cell subsets and genetic changes in this neoplasm: alterations in JAK-STAT pathway genes and mutations in epigenetic modifier genes (e.g., *TET2*, *KMT2D*) preferentially occur in CD4+, CD4+/CD8+, and CD4-/CD8- subsets, with CD4+ cases sometimes displaying *STAT3*::*JAK2* fusions. In contrast, some CD8+ cases have been shown to harbor structural alterations involving the *IL2* gene [227, 230]. **Indolent NK-cell lymphoproliferative disorder of the GI tract (iNKLPD)**, (Fig. 6) formerly known as lymphomatoid gastropathy or NK-cell enteropathy and previously thought to be a reactive process, is included as an entity because of recent findings supporting its neoplastic nature. Somatic mutations in various genes have been identified, including recurrent *JAK3* mutations (K563_C565del; NP_000206). Moreover, immunophenotypic features support a role for JAK3-STAT5 pathway activation in pathogenesis [231]. Nonetheless, the disease has a benign clinical outcome: individual lesions usually spontaneously regress in a few months, although lesions may persist or new lesions may develop over a period of years. Progression to aggressive disease is not reported, justifying its designation as "lymphoproliferative disorder" [231–233]. An interesting observation is that this tumour may not be entirely confined to the GI tract, with rare cases reported to involve gallbladder, adjacent lymph nodes and the vagina [234–236]. It is most important not to misinterpret iNKLPD as extranodal NK/T-cell lymphoma, the immunophenotype of which can be largely identical with the exception of crucial differential EBV association. While the infiltrate of atypical medium-sized lymphoid cells is worrisome, the small size and superficial nature of the lesions, expansile rather than highly destructive growth and presence of paranuclear brightly eosinophilic granules may provide a clue to the diagnosis, which can be further confirmed by the lack of EBV.

Hepatosplenic T-cell lymphoma: not confined to the young

Various new findings regarding **hepatosplenic T-cell lymphoma (HSTCL)** since WHO-HAEM4R have led to refinements in WHO-HAEM5. Recent studies have shown that HSTCL is not necessarily a disease of the young; only 49% of patients were younger than 60 years of age in a recent study [237]. Of note, dyspoiesis of bone marrow elements mimicking myelodysplastic syndrome is not uncommon in marrow smears of HSTCL patients, although this does not have any clinical impact [238]. While most cases express TCRγδ (~75%) followed by TCRαβ (~25%), a small subset of cases, about 5%, are TCR-silent [239].

Table 7. Comparison of different types of T and NK cell lymphoproliferative disorders and lymphomas involving the gastrointestinal tract (GIT).

	Indolent T-cell lymphoma of the GIT	**Indolent NK-cell LPD of the GIT**	**Enteropathy-associated T-cell lymphoma**	**Monomorphic epitheliotropic intestinal T-cell lymphoma**	**Extranodal NK/T-cell lymphoma**
Major clinical presentation	Abdominal symptoms	Asymptomatic or nonspecific GI symptoms	Abdominal symptoms; bowel perforation or obstruction common.	Abdominal symptoms; bowel perforation or obstruction common.	Abdominal symptoms; bowel perforation common.
Association with celiac disease	–	–	+	–	–
Clinical course	Chronic persistent or relapsing	Usually spontaneous regression, but may persist or develop new lesions	Aggressive	Aggressive	Aggressive
Commonest localization in GIT	Small bowel or colon	Stomach, small and large intestines	Small intestine	Small intestine	Small and large intestines
Depth of involvement	Superficial	Superficial	Deep	Deep	Deep
Cytomorphology	Small lymphoid cells with minimal nuclear atypia	Atypical medium-sized cells with pale cytoplasm and eosinophilic granules	Pleomorphic large or medium-sized cells, often with prominent inflammatory background	Monomorphic small to medium-sized cells	Variable cytomorphology, from small to medium-sized to large cells
Epitheliotropism	−/ focal	−/ minimal	+	+	–
Necrosis	–	–	+/−	Usually –	+
EBV association	–	–	–	–	+
Lineage	T cell, CD4+ >CD8+	NK cell	T cell, most often CD4-, CD8-	T cell, most often CD8+	NK cell (commoner) or T cell
Molecular genetics	*JAK2*::*STAT3* fusion; mutations of JAK-STAT pathway genes and epigenetic modifier genes	*JAK3* mutation	Gains of 9q34; loss of 16q12; mutations of JAK-STAT pathway genes (commonly *JAK1*, *STAT3*)	Gains of 9q34; loss of 16q12; mutations of *SETD2* and JAK-STAT pathway genes (commonly *JAK3, STAT5B*)	6q21-25 deletion; Mutations of JAK-STAT pathway genes, epigenetic regulators, tumor suppressor genes (*TP53*, *MGA*) and RNA helicase (*DDX3X)*

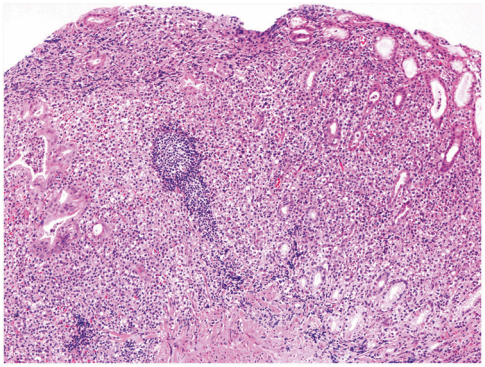

Fig. 6 Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract involving the stomach. The gastric mucosa shows expansion of the lamina propria by an atypical lymphoid infiltrate. The tumour cells are medium-sized, often with pale-staining cytoplasm.

Anaplastic large cell lymphoma: more genetic data in an otherwise well-defined entity

WHO-HAEM5 recognizes 3 entities within the family of **anaplastic large cell lymphomas (ALCL)**, which are mature T-cell lymphomas characterized by pleomorphic tumour cells with uniform strong expression of CD30 and often defective expression of T-lineage markers. Primary cutaneous ALCL is grouped under primary cutaneous T-cell lymphoid proliferations and lymphomas acknowledging its clinico-pathological relation to these disorders and highly favorable outcome in contrast to systemic ALK- ALCL [240, 241]. **ALK positive anaplastic large cell lymphoma (ALK+ ALCL)** has been separated from ALK-negative ALCL (ALK- ALCL) since WHO-HAEM4 based on its distinct pathogenesis [242, 243] and clinical course. **ALK- ALCL** was acknowledged as a heterogeneous entity. Recent genomic analyses have led to recognition of several genetic contexts with prognostic implications, although there are currently insufficient data to determine if these are best regarded as prognostic markers or molecular subtypes. ALK-negative ALCL bearing *TP63* rearrangements [244], loss of *TP53* [244–246] and/or overexpression of IL-2Rα [247] are associated with poor outcomes. Although initial reports suggested *DUSP22* rearrangement to be associated with a favorable 5-year overall survival comparable to ALK+ ALCL [248], more recent studies have not confirmed this association [249]. Some specific molecular alterations in ALK- ALCL have been shown to correlate with morphologic features. ALCLs with *DUSP22* rearrangement are characterized by neoplastic cells with a "doughnut cell" appearance [250] and sheet-like growth pattern with less pleomorphic cells; LEF1 expression may serve as a surrogate marker for this molecular alteration [251]. A subset of cases with Hodgkin-like morphology shows aberrant ERBB4 protein expression [252], while more anaplastic cells are seen in cases with *JAK2* rearrangement [253]. **Breast implant-associated ALCL** (BIA-ALCL) is an entity distinct from other ALK- ALCL; notably it is a usually non-invasive neoplasm arising in association with textured-surface breast implants and is associated with an excellent outcome [254]. Invasion of adjacent structures, however, worsens the prognosis. Recent studies highlight the importance of TH2 allergic inflammatory response, a role for immune-evasion via amplification of 9p24.1 and overexpression of PD-L1 in over 50% of the cases and constitutive JAK-STAT activation by somatic mutations of *STAT3, STAT5B, JAK1 and JAK2* and loss-of function mutations of *SOCS1* and *SOCS3* [255–261].

Nodal T-follicular helper cell lymphomas: New nomenclature to unite family members

This family includes three entities of nodal T-cell lymphomas that bear the phenotype and gene expression signatures of T-follicular helper (TFH) cells [262, 263]. While the conceptual basis for the recognition of these entities is consistent with that proposed in WHO-HAEM4R, a common family terminology of nodal T-follicular helper cell lymphomas (nTFHLs) is introduced in WHO-HAEM5, with previously recognized diseases now regarded as entities within this family. Accordingly, diseases previously referred to as "angioimmunoblastic T-cell lymphoma", "follicular T-cell lymphoma" and "peripheral T cell lymphoma with TFH phenotype" are renamed nTFHL angioimmunoblastic-type (nTFHL-AI), nTFHL follicular-type (nTFHL-F) and nTFHL not otherwise specified (nTFHL-NOS), respectively. This is to recognize their significant clinical and immunophenotypic overlap and plasticity [264, 265], as well as similar TFH gene expression signature and mutation profiles. Research in the coming years may provide data to further define the boundaries in biology between these entities or rather refute such differences. The current classification provides a platform for such studies.

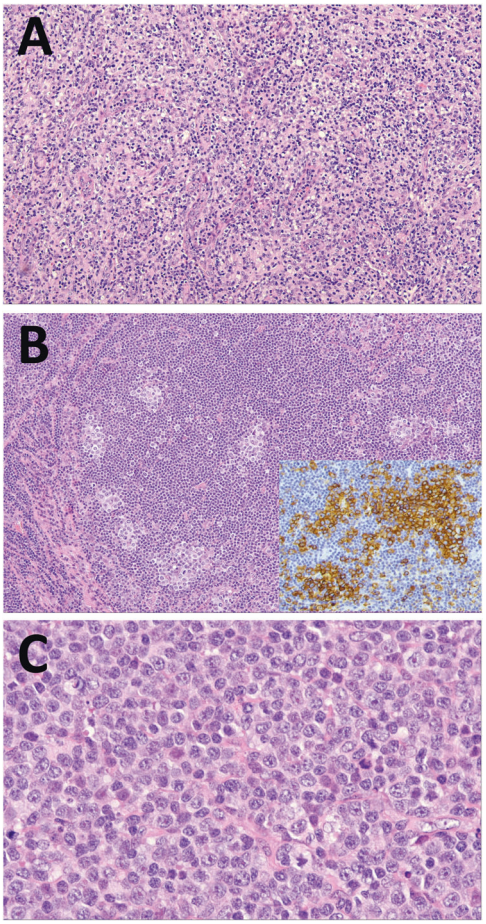

Fig. 7 Nodal TFH-cell lymphoma (nTFHL). A Nodal TFH-cell lymphoma, angioimmunoblastic-type (nTFHL-AI). The normal architecture of the lymph node is effaced. There is a diffuse infiltrate of medium-sized, slightly atypical lymphocytes, sometimes with clear cytoplasm. One of the hallmarks of the disease is the proliferation of arborizing post-capillary vessels consistent with high endothelial venules. **B** Nodal TFH-cell lymphoma, follicular-type (nTFHL-F). In this example, progressive transformation of germinal centre-like nTFHL-F, clusters of atypical lymphoid cells with pale cytoplasm are embedded in a background of small lymphocytes of mantle zone type. The inset shows strong expression of PD1 in the tumour cells. **C** Nodal TFH-cell lymphoma, not otherwise specified. This tumour is composed of a sheet-like proliferation of medium-sized to large neoplastic cells.

Nodal T-follicular helper cell lymphoma, angioimmunoblastic-type (nTFHL-AI) is the prototype with well-defined clinical,

morphologic (Fig. 7), immunophenotypic and characteristic mutational profiles. Genetically, nTFHL-AI is characterized by a stepwise acquisition of somatic changes with *TET2* and *DNMT3A* mutations occurring early in haematopoietic stem cells, while *RHOA* and *IDH2* mutations are also present in the neoplastic TFH cell population. In contrast, **nTFHL-F** and **nTFHL-NOS** (Fig. 7) represent less well-studied nodal lymphomas, which also express TFH markers such as PD1, ICOS, CXCL13, CD10, and BCL6 [266–277] and show mutation profiles similar to those of nTFHL-AI [265, 266, 278–280].

Although the individual entities are defined predominantly by histopathological features, there is considerable morphologic overlap and inter-observer variability. nTFHL-NOS is the recommended term for CD4+ lymphomas with TFH phenotype but that do not meet criteria for nTFHL-AI or nTFHL-F. The generic term nTFHL rather than nTFHL-NOS is recommended when interpreting core biopsies to prevent misclassification due to inadequate sampling. The TFH phenotype is defined as the presence of at least two TFH markers in addition to CD4. Further studies are required to determine if this definition is sufficiently robust in differentiating nTFHL-NOS from PTCL, NOS, as most cases of the former often express the less specific TFH markers such as PD1 and ICOS. In essence, the diagnosis may be challenging with many pitfalls. An integrated approach is recommended, at the very minimum requiring correlation of clinical, morphologic and immunophenotypic features, with input from genomics for clonality and mutational profiles in difficult cases.

Other peripheral T-cell and NK-cell lymphomas: nodal EBV+ T- and NK-cell lymphoma counterpart of extranodal NK/T-cell lymphoma

In WHO-HAEM5, **peripheral T-cell lymphoma NOS (PTCL-NOS)** remains a heterogeneous category and a diagnosis of exclusion, with a differential diagnosis that in particular includes nodal T-follicular helper cell lymphomas, among others. Two possible biological variants of PTCL-NOS, PTCL-TBX21 and PTCL-GATA3, have been characterized by the transcriptional program of T-helper-1 and T-helper-2 cells, respectively [281]. While PTCL-GATA3 has a uniform molecular genetic profile, PTCL-TBX21 is heterogeneous and may include a subgroup with a cytotoxic gene expression program and aggressive behavior [281, 282]. The current status of knowledge on the genetic landscape, clinicopathological context and prognostic implications of these possible biological variants of PTCL-NOS are deemed, however, insufficient to justify a formal status as "subtype" [283]. **Extranodal NK/T-cell lymphoma (ENKTL)** will have the qualifier "nasal-type" dropped from its name in WHO-HAEM5 in accordance with the recognized presentation of this disease at various extranodal sites. The introduction of L-asparaginase-based chemotherapy in combination with radiotherapy has led to markedly improved outcomes for this lymphoma [284]. Immune checkpoint inhibitor therapy has recently shown great promise for relapsed or refractory disease [285–287], in keeping with the finding that immune evasion is a critical pathway for ENKTL cell survival [288, 289]. **Intravascular NK/T-cell lymphoma** was considered a form of ENKTL in WHO-HAEM4R [290–295]. This highly aggressive lymphoma is often, but not invariably, EBV positive, does not present with mass lesions and shows a predilection for skin and central nervous system. Since its nosological nature is still unclear, it is now described under aggressive NK-cell leukaemia rather than extranodal NK/T-cell lymphomas, pending further studies to determine where it fits best.

Nodal EBV-positive T and NK-cell lymphoma, which occurs mostly in East Asians [296–300], is now recognized as a distinct entity in WHO-HAEM5; previously it was subsumed as a subtype under the entity of PTCL-NOS. Patients typically present with lymphadenopathy with or without extranodal involvement, advanced-stage disease and B symptoms; they have a dismal prognosis. Morphologically, this lymphoma often resembles diffuse large B-cell lymphoma, lacking the coagulative necrosis and angioinvasion characteristic of ENKTL (Fig. 8). It more often shows a cytotoxic T-cell than NK-cell immunophenotype; EBV is positive, by definition. The genetic landscape differs from that of ENKTL, with the most commonly mutated gene being *TET2* [300].

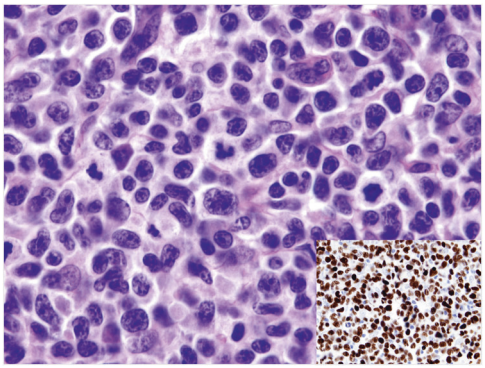

Fig. 8 Nodal EBV-positive T- and NK-cell lymphoma. This lymphoma shows a diffuse infiltrate of relatively monotonous, medium-sized to large cells, sometimes reminiscent of centroblasts. Inset: in-situ hybridization for EBERs identifies EBV infection in virtually all tumour cells.

EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood: revised terminology

EBV-associated lymphoid proliferations and lymphomas of childhood are uncommon T- and NK-cell disorders with a predilection for Asian and native American ethnic groups [301–305]; occurrence in adults is also reported [306]. This family includes **chronic active EBV disease (CAEBVD) and systemic EBV-positive T-cell lymphoma of childhood**. CAEBVD is characterized by a broad clinical spectrum varying from localized and/or indolent forms (**severe mosquito bite allergy** and **hydroa vacciniforme lymphoproliferative disorder [HVLPD] classic form**), to systemic disease with fever, hepatosplenomegaly, and lymphadenopathy, with or without cutaneous manifestations (**HVLPD systemic form** and **systemic CAEBVD**).

This classification introduces several changes in terminology to reflect the morphologic overlap among different entities, such as HVLPD systemic form and systemic CAEBVD, and the need for clinicopathologic correlation in diagnosis. "Hydroa vacciniforme-like lymphoproliferative disorder" in WHO-HAEM4R has been renamed HVLPD, with identification of a classic and a systemic form. Systemic HVLPD shows persistent systemic symptoms of CAEBVD or extracutaneous disease, and should be distinguished from systemic CAEBVD without HVLPD, which is characteried by an even more aggressive clinical course [307–310]. Moreover, the usually fatal outcome in the absence of haematopoietic stem cell transplantation has led to replacement of the former terminology "chronic active EBV **infection**, systemic form" with "systemic chronic active EBV **disease**" [308, 309].

Stroma-derived neoplasms of lymphoid tissues: some tumour types are unique to lymph node or spleen

A new category of stroma-derived neoplasms of lymphoid tissues is introduced in WHO-HAEM5 (Table 3). Mesenchymal tumours specific to lymph node (including **intranodal palisaded myofibroblastoma)** and spleen (including **littoral cell angioma, splenic hamartoma and sclerosing angiomatoid nodular transformation)** are covered, while various soft tissue tumours not specific to lymph node or spleen (such as haemangioma, lymphangiomyoma, Kaposi sarcoma and angiosarcoma) are covered in the WHO Classification of Soft Tissue and Bone Tumours (5th edition, 2020). Furthermore, follicular dendritic cell and fibroblastic reticular cell neoplasms have been moved from the "histiocytic and dendritic cell neoplasms" category

to this new category, because follicular dendritic cells are not derived from haematopoietic stem cells but rather are of mesenchymal origin [311–313]. Given its distinctive clinicopathologic features, **EBV-positive inflammatory follicular dendritic cell sarcoma** is delineated as an entity separate from follicular dendritic cell sarcoma [314], together with a nomenclature change from "inflammatory pseudotumour-like follicular/fibroblastic dendritic cell sarcoma", a change first introduced in the WHO Classification of Digestive Tract Tumours (5th edition, 2019) [315].

Genetic predisposition syndromes: increasing importance of germline genetics

To acknowledge the growing number of known germline predispositions associated with haematologic neoplasms, lymphoid neoplasms occurring in the context of clinical syndromes should be separately recognized, similar to classification in other organ systems. To this end, WHO-HAEM5 introduces new chapters on genetic predisposition. With regard to lymphoid neoplasms, Ataxia telangiectasia (AT) and Nijmegen-Breakage syndrome are particularly relevant. These are linked to germline mutations in *ATM* and *NBN*, respectively. The detection of such underlying syndromes associated with germline predisposition is clinically important not only with regards to treatment planning (e.g., increased toxicities) but also surveillance of carriers and counselling of relatives. In this regard, leukaemias and lymphomas should be diagnosed using conventional criteria but should be designated as "AT-related" or "NBS-related". Besides the separate chapter on genetic predisposition syndromes, aspects of germline predisposition including recommendations for germline testing have been systematically incorporated in individual chapters.

Epilogue

The dramatic increase in information regarding lymphoid tumours and their molecular complexity suggests that Fyodor Dostoyevsky's famous words [316], "*Reality is infinitely diverse (…and) Reality resists classification*" hold true for lymphoma classifications.

We are aware that any classification is arbitrary and subject to further evolution as new evidence arises. Moreover, since the development and differentiation of lymphocytes represent a continuous spectrum rather than a sequence of distinct steps, we acknowledge that any classification system breaks up a disease continuum into groups using arbitrary (and yet evidence-based) borders. Furthermore, our daily work demands the naming, and hence, the diagnosis, of discrete entities to allow for treatment decisions and for patient management. Therefore, following the principles of Linnaeus, classification also provides the basis for preserving knowledge and providing a template for future work.

We are grateful to - and stand on the shoulders of - countless individuals and research teams, who have contributed significantly to establish the foundations of the current lymphoma classification. We thank the numerous authors and contributors whose input and thoughts have created the herein outlined 'snapshot-in-time' of the classification. We are confident that the present proposal, albeit by definition imperfect, will provide a robust framework for future generations of scientists to continue our efforts, to further disentangle the universe of lymphoma biology, for the benefit of patient care.

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