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The 2022 classifications of B-cell lymphomas and plasma cell disorders

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Abstract

Tumors derived from B-lymphocytes at their various stage of maturation and differentiation (human B-cell lymphomas and leukemias) are the commonest hematological malignancies. Previous editions of the World Health Organization (WHO) classification of Hematopoietic and lymphoid neoplasms, edited in 2001, 2008, and 2017, intended to standardize the diagnosis of hemopoietic neoplasms overall.

Recent advances in lymphoma research, mostly based on genomic as well as molecular analyses, have dramatically expanded our knowledge of lymphoma biology, this leading to improved diagnostic criteria, upgrading of provisional entities, and identification of new tumor types.

In 2022, two frameworks for classifying hematolymphoid neoplasms were proposed: the WHO-HAEM5 and the International Consensus Classification (ICC). Since a common nosography is essential for advancing health science and providing a foundation for precision medicine, it is critical to recognize possible differences and harmonize the diverse approaches. In this article, the Authors summarizes the key differences between the two most recent classifications by focusing on tumors derived from B-lymphocytes and plasma cells.

Introduction

Hematological neoplasms have been classified in a variety of ways, mostly based on histology and distinct tissue architecture, with some differences sometimes based on geographic regions (such as Europe vs. the USA). The International Consensus Classification (ICC) and the fifth edition of the WHO classification (WHO-HAEM-5) are the two most recent updated classifications that are now accessible for both lymphoid and myeloid neoplasms. These two different updates continue to classify hematopoietic neoplasms by integrating morphology (cytology, histology, tissue architecture), clinical attributes (e.g., acute versus chronic, cytopenias/cytoses), lineage (based on immunophenotype), and cytogenetic/molecular features. (1-4)

Lymphoid neoplasms are a heterogeneous group of lymphoproliferative disorders originating from B and T lymphocytes. B-cell lymphomas can arise at any stage of normal B-cell development, but most are derived from germinal center cells. (5) Both the ICC and the WHO-HAEM5 initially categorize lymphoid malignancies based on their immunophenotype. This distinguishes B-cell lineage versus T- and NK-cell-associated neoplasms. These categories are then further divided into precursor neoplasms and mature neoplasms. The general classifications of lymphoid malignancies in ICC and WHO-HAEM5 remain largely unchanged from the previous WHO-HAEM4R. However, both methods involve some modifications to the classification and nomenclature of certain lymphoid neoplasms. (1, 2, 6)

Among the main striking differences between the two classifications (1, 2), a new category of tumors and tumor-like lesions, predominantly composed of B cells, has been added to the list of WHO-HAEM5. It is called "Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation". Additionally, two new categories of lymphoid malignancies have been included: "Transformations of indolent B cell lymphomas" and "Primary large B cell lymphoma of immune-privileged sites." Furthermore, two rare entities from WHO-HEAM4R, "Hairy cell leukemia variant" (a provisional entity) and "B prolymphocytic leukemia," were combined to become "Splenic B cell lymphoma/leukemia with prominent nucleoli" by WHO-HAEM5.On the other hand, ICC retained "B prolymphocytic leukemia" and "Hairy cell leukemia variant" (a provisional entity).

In the following, the Authors revised the WHO-HAEM5 and ICC 2022 schemes, highlighting the main differences between them, by focusing on mature B-cell lymphoma and plasma cell disorders. To facilitate clinical use, we identified and described five major groups, namely pre-neoplastic lesion, indolent B-NHL, aggressive B-NHL, HL, and plasma cell disorders. KSV/HHV8 associated lymphoproliferative diseases will be discussed apart, as includes entities with remarkable different clinical aggressiveness.

Pre-neoplastic lesions and processes of still undetermined malignancy of B-lymphocytes

Monoclonal B-cell lymphocytosis

Monoclonal B-cell lymphocytosis (MBL) is a condition characterize by the presence of monoclonal B-cells in the peripheral blood (PB), but without reaching the value 5 x 10^9/L, in absence of any other symptoms/sign of B-cell lymphoproliferative disease (7). In the WHO-HAEM5 it is classified into three categories (low-count MBL or clonal B-cell expansion, CLL/SLL-type MBL, and non-CLL/SLL-type MBL). In the ICC, by contrast, it is classified into two categories (CLL-type and non-CLL type) (table 1). Individuals with CLL-type MBL present with above 2 x 10^9/L CD5+/CD19+ B-lymphocytes and may experience a gradual increase in their counts over time. The likelihood of requiring therapy for progressive CLL is still relatively low. (8) Non-CLL/SLL-type MBL is a monoclonal B-cell growth characterized by non-CLL immunophenotype and absence of any symptoms or signs of another mature B-cell neoplasm, and it is typically associated with marginal zone origin. (9)

In situ mantle cell neoplasm (ISMCN)(WHO-HEAM5)/In situ Mantle cell neoplasia ICC

“In situ MCL” is an extremely rare tumor, a few cases are described in the literature. Because of its rarity, its clinical behavior is still unclear. (10) It is characterized by the proliferation of the mantle zones of lymphoid follicles by B cells harboring an *IGH-CCND1* fusion resulting in cyclin D1 overexpression. (11)

There is still debate surrounding the meaning of "in situ MCL" - whether it is an early MCL colonization or a precursor lesion. However, research has shown that patients with incidentally identified "in situ MCL" do not develop an overt illness, regardless of whether therapy is administered or not. In some cases, "in situ MCL" is discovered retroactively years before overt MCL is detected. (12) It is crucial to differentiate between these two groups to decide the best therapeutic approach. (10, 13)

WHO-HAEM5 adopted the termnology in situ mantle cell neoplasm (ISMCN). On the other hand, ICC retained the old name of in situ mantle cell neoplasia. (1, 2)

Indolent B-NHL

B-Chronic lymphocytic leukemia/small lymphocytic lymphoma

CLL/SLL is a malignancy of small, mature lymphocytes that can present either as a leukemia (CLL) or a corresponding lymphoma (SLL). Diagnostic criteria for CLL/SLL are the same in ICC and WHO-HAEM5 and are based on the detection of crucial immunophenotypic markers namely CD19, CD5, CD23, $CD20^{dim}$ and surface or cytoplasmic kappa and lambda light chains. Other immunophenotypic markers may be used to differentiate CLL cases from other small B-cell lymphomas/leukemia like CD10, CD43, CD79B, CD81, CD200, and ROR1.(14)

Karyotypic analysis for chromosomal abnormalities like del(11q), del(13q), del(17p), and trisomy 12, mutational status of *TP53* gene and immunoglobulin gene heavy chain variable (*IGHV*) region somatic hypermutation (SHM) are considered crucial for prognosis and choice of therapy (15, 16). Mutations of *NOTCH1*, *SF3B1*, and *BIRC3* may carry prognostic importance but they remain optional in the diagnostic workup (17). In the future, these mutations may be included in a more refined prognostic scores index. (18).

It is crucial to differentiate between diffuse large B-cell (Richter) transformation and accelerated CLL. The first involves sheets of large cells, rather than only increased proliferation sites, enriched in prolymphocytes and paraimmunoblasts. Recently, reversible sheet proliferations of huge have been discovered in CLL patients treated with ibrutinib after sudden stoppage of treatment but it is found to be reversible after reintroduction of ibrutinib. (19-21).

B-cell prolymphocytic leukemia (ICC)

B-cell prolymphocytic leukemia (B-PLL) is a rare mature B-cell tumor that often carries a decimal prognosis. (22) Males are significantly more likely than females to have B-PLL, which predominantly affects elderly people. B-PLL are found to have greater than 55%

prolymphocytes in the PB, and typically present with huge splenomegaly, bone marrow involvement, and lymphocytosis. (23, 24)

In WHO-HAEM5, B-PLL has been removed and has been added under the title "splenic B-cell leukemia with prominent nucleoli" (SBLPN). (2) On the Other hand, ICC retained this entity but they recommended it be differentiated from other disease categories such as PLL progressed from CLL, MCL, HCLv, and splenic marginal zone lymphoma (SMZL) so cases must lack cyclinD1 and SOX1 expression, hairy cell projection, and history of CLL illness. (1)

Splenic B-cell lymphomas and leukemias

Hairy cell leukemia

Hairy cell leukemia (HCL) is a rare mature B-cell leukemia; despite the cell of origin still unclear, the transcriptional profile resembles memory B-cells. HCL carries distinctive clinicopathological criteria. A meticulous examination of the peripheral blood smear constitutes the initial stage in the distinctive morphological recognition of hairy cells and a trephine bone marrow biopsy is mandatory to determine tumor infiltration with a typical fried egg appearance. HCL cells are typically CD11c, CD103, CD123, and CD25 positive for An immunological score was proposed which consists of four markers (CD11c, CD103, CD123, and CD25), with one point given to each of them when it is expressed and no point when it is not expressed. A score of 3 or 4 is observed in 98% of cases of HCL.(25, 26). $BRAF^{V600E}$ somatic mutation is the driver oncogenic mutation in most cases of HCL and it carries therapeutic application.

Both WHO-HEAM5 and ICC don't change the nomenclature or the diagnostic criteria of HCL.

Splenic marginal zone lymphoma

Splenic marginal zone lymphoma (SMZL) is a small B-cell lymphoma, and it has been categorized as a single entity by WHO since 2008. The disease is primarily diagnosed based on the gradual onset of spleen enlargement, which may be accompanied by autoimmune

disorders like autoimmune hemolytic anemia or abnormalities in the complete blood count (AIHA) causing cytopenia. The disease progresses slowly and is typically observed in individuals above the age of 67 years. After ten years, the survival rates range from 67% to 95%.(27, 28) Flow cytometry analysis showed that the cells are FMC7+, CD24+, and CD27+. They may not be as bright as other types of splenic lymphomas, such as splenic diffuse red pulp small B-cell lymphoma or HCL, but they typically react to CD22 and CD11c. While the CD103 is sometimes faintly positive, the CD123 is always negative. Annexin A1 and CD25 are usually negative in such cases, regardless of the analytical method used.CD180 is a useful immunologic marker in MZL. Additionally, the staining intensity of CD180 may suggest a splenic origin for the lymphoma since SMZL and SDRPL express high levels of it. (29, 30)

At genetics, few recurrent abnormalities have been observed, distinct from other B-cell lymphomas. The most common is 7q deletions, occurring in 30-40% of cases. (31) However, recently, next generation sequencing allowed the identification of a number of additional gene mutations affecting *NOTCH2* (10–25% of cases), *KLF2* (20–30%), *TP53* (10–15%), and mutations affecting the NFκB pathway like *CARD11, TNFAIP3, TRAF3, or BIRC3* (32, 33).

The definition of SMZL in ICC and WHO-HAEM5 remains unchanged.(1, 2)

Splenic diffuse red pulp small B-cell lymphoma (SDRPL)

Splenic diffuse red pulp small B-cell lymphoma (SDRPL) is a rare primary splenic non-Hodgkin's lymphoma (NHL) that can affect peripheral blood, bone marrow, and the red pulp of the spleen. It is composed of small B-lymphocytes. Initially recognized as a distinct entity in the 2008 WHO classification of lymphoid neoplasms, SDRPL was classified as a provisional group. (34)

Clinically it is characterized by splenomegaly, lymphocytosis, and cytopenia. The diagnosis of SDRPL relies on splenic histology (red pulp with blood lakes) and immunohistochemistry, although a positive immunophenotype in bone marrow (BM) with a purely intra-sinusoidal pattern or in peripheral blood (PB) with the predominance of villous lymphocytes can also suggest the diagnosis. (35) It is crucial to differentiate SDRPL from other primary splenic

lymphomas because it exhibits several clinical and laboratory characteristics in common with HCL, SMZL, and HCL variant (HCL-v).

SDRPL is Immunophenotypiically characterized by CD20, DBA.44 (20 to 90%), and IgG expression, while it is typically negative for CD5, CD10, CD23, cyclin D1, CD43, annexin A1, CD11c, CD25, CD123. Most SDRPL express cyclin D3, distinguishing it from other B-cell lymphomas.(35, 36)

SDRPL is considered an entity in WHO-HAEM5 and a provisional entity in ICC.(1, 2)

Splenic B cell lymphoma/leukemia with prominent nucleoli (SBLPN)(WHO-HEAM5)

Splenic B cell lymphoma/ leukemia with prominent nucleoli (SBLPN) is a new entity introduced by WHO-HEAM5 including the previous term hairy cell leukemia variant and CD5 negative prolymphocytic leukemia. This entity is not included in ICC. SBLPN is an uncommon entity that is often CD25-negative on flow cytometry. However, mutational analysis (e.g., *BRAFV600E)* can aid in distinguishing SBLPN from HCL in dim CD25-positive cases. (37) (38).

Lymphoplasmacytic lymphoma

Lymphoplasmacytic lymphoma (LPL) is defined as a mature B-cell neoplasm that consists of a mixture of tiny B lymphocytes, plasma cells, and plasmacytoid lymphocytes. (39, 40)

WHO-HAEM5 classified LPL into two types,namely Waldenström macroglobulinaemia (WM) and Non-Waldenström macroglobulinaemia (including cases with IgG or IgA monoclonal proteins, non-secretory LPL, and IgM-LPL without BM involvement). Waldenström macroglobulinaemia (WM) usually comes with bone marrow involvement, the presence of an IgM monoclonal paraprotein, and hyperviscosity, whereas lymph nodes and spleen are rarely involved. On the other hand, LPL of non-WM is rare and mainly composed of cases without bone marrow involvement and/or the absence of IgM protein. (39) WM can be associated with hepatitis C infection, as well as type II cryoglobulinemia. (41)

At immunophenotyping, LPL typically expresses IgM+, CD5+/-, CD10-, CD19+, CD20+, CD22+, CD23-, CD25+, CD27+, and FMC7+, with CD103-, CD138-. The plasmacytic component is CD138+, CD38+, and CD45- or dim.(42)

MYD88 L265P mutation is considered to be the hallmark and the driver mutation in 90% of WM-LPL cases and it is an essential marker in the differential diagnosis between it and plasma cell myeloma and other small cell lymphoma. (43) Cases with *MYD88* mutation and *CXCR4* mutations (30 - 40%) are associated with drug resistance and heavily infiltrated bone marrow involvement. (44)

According to the ICC, LPL can be diagnosed even when neoplastic cells clusters represent less than 10% in trephine bone marrow biopsy, while in the WHO-HAEM5 LPL could be diagnosed only when clonal lymphoplasmacytic aggregates represented ≥10% of BM cellularity in trephine biopsies. (1, 2)

Extranodal marginal zone lymphoma and nodal MZL

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) can occur in various locations and is often linked to autoimmune conditions (e.g. Sjögren syndrome and Hashimoto thyroiditis) resulting in inflammatory lymphoid populations or chronic antigenic stimulation by infectious pathogens. Gastric MALT is the most common site, other common sites include the ocular adnexa, salivary glands, skin, conjunctiva, lungs, thyroid, and breasts. (45, 46). The diagnosis of MALT lymphoma largely depends on histopathological examination and immunohistochemical staining, morphologically, the neoplastic cells are usually heterogeneous small to medium-sized cells ranging from lymphocyte- and centrocyte-like to monocytoid with some plasma cell differentiation. At the mucosal sites, the malignant cells form a pathognomonic feature called the lympho-epithelial lesions, follicular colonization are also may be observed. The clonal cells are usually positive for B-cell antigens including CD19, CD20, CD22, CD79a and

CD79b, and are negative for CD5, CD3, CD23, CD11c and CD10. The only specific marker is IRTA1, typically expressed by MZL (47).

Despite the heterogeneity of the etiological factors, the anatomical sites of presentation, and the treatment approach, both ICC and WHO-HAEM5 continue not to classify MALT lymphoma according to the site except for cutaneous type which is considered now as a new entity in both of the classification systems. (1, 2)

Nodal Marginal Zone Lymphoma

Nodal MZL is the least prevalent of all the subtypes of MZL, the disease generally behaves in an indolent but disseminated fashion. Histological transformation is found in 3-15% of patients with nodal MZL and is often associated with a poor outcome. (46)

Clinically, Nodal marginal zone lymphoma patients often have lymphadenopathy and splenic involvement, which can make it difficult to differentiate from SMZL. Immunostaining for IRTA1 may help in differential diagnosis. (48) These patients also exhibit IgM paraproteinemia without the presence of a *MYD88* mutation. It has been found that 20% of individuals with nodal MZL have *PTPRD* mutations, which appears to be a unique characteristic of this particular form of lymphoma. (49-51)

There are no changes in both classifications regarding the nomenclature and the diagnostic criteria of Nodal MZL.(1, 2)

Pediatric nodal marginal zone lymphoma (pNMZL)

Pediatric nodal marginal zone lymphoma is one of the rarest B-cell lymphomas and is now considered a distinct entity on WHO-HEAM5 but it is still considered a provisional entity in ICC.(1, 2). Although they are more commonly observed in children, they can also occur in adults. (52, 53) It shows overlapping features with pediatric-type follicular lymphoma, but they cannot be grouped under the same entity.

In children, a male predominance is observed and most cases are asymptomatic with localized (stage I) disease, low relapse rates, and an excellent outcome. (54) Therapeutic approaches

used, (observation alone, surgical resection, chemotherapy, radiotherapy, steroids, antibiotics, and rituximab), overall survival remains 100%, suggesting that both MZLs are curable in children. (55)

Primary cutaneous marginal zone lymphoma (PCMZL)(WHO-HEAM5)/ primary cutaneous marginal zone lymphoproliferative disorder (ICC)

Diagnosing primary cutaneous marginal zone lymphoma (PCMZL), which is one of the major subtypes of primary cutaneous B-cell lymphoma, can pose a challenge due to the inclusion of benign cutaneous lymphoproliferations as well as other primary or secondary cutaneous B-cell or T-cell lymphomas in the differential diagnosis. (56)

PCMZLs typically involve the skin without evidence of extracutaneous spread at the time of diagnosis. PCMZL usually occurs with red-violaceous, small, solitary, or multiple papules or nodules and rarely plaques with very indolent course, preferentially located on the trunk, arms, and occasionally the head. transformation to higher grade NLH is reported and it is associated with decimal outcome. Histologically, PCMZL is characterized by a dense dermal lymphoid infiltrate, which is most often arranged in a vaguely nodular or diffuse pattern. The infiltrate usually fulfills the dermis and extends to the hypodermis. Neoplastic cells are CD20+, CD79A+, BCL2 + CD5-, CD10-, and BCL6- . PCMZL has two subtypes according to the type of cellular infiltrates and CXCR3 expression. (57, 58)

According to the EORTC/ISCL recommendation, people with one or a few nearby tumors may find radiation therapy or surgery helpful, to be curative. Low-dose radiation therapy (LDRT) (4 Gy) may be preferred due to its high response rates and ability to minimize acute toxicity. (57) Patients can also be treated with an antibiotic regimen against Borrelia which is involved as an etiological factor in PCMZL lymphogenesis. (59)

ICC refers to PCMZLs as “primary cutaneous marginal zone lymphoproliferative disorder”, avoiding the term lymphoma due to its indolent behavior, long term survival with non-intensive therapy, and usually localized spread; cutaneous recurrences, however, are not rare. In the WHO-HAEM5, the term “PCMZL” was maintained.(1, 2)

Follicular lymphoma

Follicular lymphoma (FL) is the second most common type of lymphoma worldwide, displaying germinal center origin (60). Unfortunately, conventional chemotherapy is not very effective in curing the disease, despite its generally slow-growing nature. Even after the initial clinical remission, the disease tends to come back, become resistant to medication, and in some rare cases, progress into a secondary diffuse large B-cell lymphoma. (61, 62)

WHO-HEAM5 updated the terminology “in situ follicular neoplasia” into “in situ follicular neoplasm”, while in the ICC the name remained unchanged.(2)

According to WHO-HEAM5 follicular lymphoma is classified into 3 subtypes:

1. classic FL (cFL) which represents the vast majority of cases and harbours t14;18), with at least partial follicular growth pattern;
2. follicular large B-cell lymphoma (FLBL), largely overlapping with previously named FL grade 3B;
3. FL with uncommon features (uFL), which is further subdivided into two subtypes:
    - FL with blastoid features;
    - FL with predominantly diffuse growth pattern.

The histologic grading system for classical follicular lymphoma is not included in WHO-HAEM5, this major revision was based on a massive literature review and experts' opinions as it was found that the molecular profile of follicular lymphoma is intimately related to that of normal centrocytes, irrespectively of the histological grade, with a definite homogenous gene expression profile (60). Additionally, this grading system is based on enumeration of centroblast per high-power field (HPF) it is very descriptive as it may be affected by the type of sample whatever excisional or core needle biopsy, and method of identification and enumeration of the centroblasts (63-65).

On the other hand, the ICC retained the histologic grading of classical follicular lymphoma, and introduced two new definitions (1):

1. *BCL2*-R-negative, CD23-positive follicle center lymphoma (provisional entity) which corresponds to FL with predominantly diffuse pattern in WHO-HEAM5;
2. Testicular follicular lymphoma, as separate entity from pediatric follicular lymphoma.

Both classifications pointed out the relevance of the so called POD24 (progression of disease within 24 months). These patients represent the major challenge in FL treatment and identification of reliable biomarkers is a main need for future studies. Remarkably, FL grade 3B, for long time debated whether to belong to FL or to DLBCL chapters, was eventually confirmed to be a FL, as already indicated by gene expression profiling (60).

Pediatric follicular lymphoma duodenal lymphoma and cutaneous follicle lymphoma are the same in both ICC and WHO-HAEM5.(1, 2)

Aggressive Lymphomas

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a B-NHL with a mainly aggressive but heterogeneous, clinical course. MCL accounts for 3% to 10% of adult NHL.(10, 13)

The occurrence and proliferation of MCL clones is mediated by a complex interplay of cellular and microenvironmental factors; the first include *CCND1* (Cyclin D1*)* overexpression, which represents the hallmark of the MCL biology, *SOX11* overexpression, *TP53* mutations, and other recently discovered molecular alterations such as chromosomal complexity, *NSD2, NOTCH2, UBR5, BIRC3, TRAF2, MAP2K14, KMT2D, CARD11, SMARCA4*, and *BTK* that have been linked to target therapy resistance (66). Additionally, tissue microenvironment plays a crucial role in the survival of MCL clones. In MCL patients, the microenvironment of

lymph nodes differs from that of peripheral blood, showing a distinct expression of genes associated with canonical NFkB pathways and BCR signaling. (67)

Regarding The WHO-HEAM5 and The ICC, there is no major update in the diagnostic criteria or the nomenclature of MCL (1, 2).

Non-nodal MCL (nnMCL)

Non-nodal MCL (nnMCL) is the "indolent" variant of MCL, as recognized by both WHO-HEM5 and ICC. It is characterized by a less aggressive clinical course than MCL, blood, and bone marrow involvement without nodal involvement. The malignant clones show negativity for *SOX11* expression, *ATM* mutations/deletions, or *TP53* mutations and a high load of somatic *IGH* hypermutations.

nnMCL can progress to cMCL with an aggressive clinical course when it acquires subclonal mutations like *TP53* or *ATM*.(68-71)

High-grade transformation of indolent lymphoma

For the first time, WHO-HEAM5 introduced a new entity named high -grade transformation of indolent B cell lymphoma. It includes all secondary aggressive lymphomas derived from a transformation of a previously identified lymphoma.

One of the indicators of a poor outcome in the progression of indolent lymphomas like CLL and FL is when it transforms into an aggressive lymphoma, usually diffuse large-cell B-lymphoma (DLBCL) (72). Upon transformation, the immunophenotype of the original lymphoma is often preserved. The transformation can be associated with disease spread throughout the body. Signs of transformation may include enlarged lymph nodes, elevated levels of LDH, and systemic symptoms. A tissue architecture observation is necessary to confirm the diagnosis of transformation, and fine needle aspiration biopsy is not sufficient for this purpose.

This entity is not listed by ICC (1).

Large B cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), NOS remains the commonest aggressive lymphoma and the commonest overall. It is recognized that the current knowledge still fails to unequivocally distinguish different diseases that probably coexist under the umbrella of the term DLBCL/NOS. However, there is some evidence that based on genetic and transcriptional profiles, this entity can be better stratified.

In addition, the WHO-HAEM5 recognizes 17 specific entities as “large B-cell lymphomas” other than DLBCL, NOS.(2) Despite not substantially changed from WHO-HAEM4R, certain entities' names have changed for uniformity, from "diffuse large B-cell lymphoma" to "large B-cell lymphoma," recognizing that a diffuse growth pattern is either not noticeable or present, or it is not evaluated in some categories. (2)

Diffuse large B-cell lymphoma (DLBCL), NOS

DLBCL is the commonest lymphoma subtype and accounts for nearly 35 percent of all NHLs in developed countries. (73) DLBCL is mainly composed of large-sized (unusually medium-sized) B lymphoid cells, with large nuclei, usually more than twice as large as those of normal lymphocytes. The growth pattern is by definition diffuse with extensive tissue architecture effacement.

DLBCL, not otherwise specified (NOS) accounts for most cases and it’s highly heterogeneous in terms of morphology, genetics, and clinical characteristics. Morphological variants (pleomorphic, centroblastic, immunoblastic, anaplastic, and other rare variants) are relevant for differential diagnosis but do not impact either patients’ management or clinical outcome. Conversely, the differentiation based on transcriptomic profiles, related to different cellular counterparts is provided with clinical relevance. Based on that, both WHO-HEM5 and ICC confirmed the existence of the two molecular subgroups, namely germinal center B-cell type

(GCB, corresponding to germinal center cells) and activated B-cell type (ABC, related to a slightly more advanced differentiation, such as plasmablasts). Despite this distinction was originally referred to diverse cell of origin (COO), there is no formal evidence for that. In fact, all DLBCL are likely to be originated within the germinal centers, mostly due to aberrant somatic hypermutations (74). Rather, they correspond to different cellular counterparts based on different abilities to progress into the differentiation process. As a matter of fact, ABC-type, supposed to derive from plasmablasts, does not even reach the morphological features of plasmablasts but only acquires part of their transcriptional programs and, consequently, some of (but not all) their immunophenotypic properties.

As far as genetic is concerned, over 150 genes were described to be recurrently mutated; however, the relevance of particular genetic subgroups is not well-established yet. Additional data from clinical studies will be needed to determine the effect of these genetic clusters on outcomes and as the foundation for focused treatment strategies. Consequently, the introduction of such molecular classifications was deemed premature but it is considered mandatory in the near future. (75)

Large B-cell lymphomas (LBCL) of immune-privileged sites

According to the WHO-HEAM5, large B-cell lymphomas (LBCL) of immune-privileged (IP) sites are a group of aggressive lymphomas that share common biological characteristics as they occur as primary tumors in immunologically atypical sites, like the vitreoretinal compartment, the central nervous system (CNS), and the testes of otherwise immunocompetent patients (2). In WHO-HAEM4, those entities were grouped within DLBCL/NOS.

ICC considered primary DLBCL of the testis as a distinct entity but they agreed that subcategorization of this group of large cell lymphoma is a reasonable proposal (1).

Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (WHO-HAEM5)/ High grade B-cell lymphoma with MYC and BCL2 rearrangements (ICC)

Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements are a group of tumors that characterized by the presence of both *MYC* and *BCL2* rearrangements that may be composed of large or intermediate or blastoid cells. This group of cases is homogeneous, clinically highly aggressive, often displaying GCB-type DLBCL features and a close pathogenetic link to FL (2). In ICC its name remained high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. (1)

The recognition of these lymphomas is based on genetics (usually FISH) and BCL2-MYC coexpression is not sufficient for a diagnosis (those would rather be, DLBCL/NOS, "double expressor"), and relevant as they are provided with extremely severe prognosis if conventional chemotherapy like R-CHOP is used. It seems reasonable to apply *BCL2* and *MYC* FISH only to cases that present expression of the encoded proteins at immunohistochemistry.

Of note, *BCL6* translocations are not considered any longer relevant in this regard and the previously recognized triple hit lymphomas are not listed in recent classifications.

High-grade B-cell lymphoma with 11q aberration (WHO-HEAM5)/ large B-cell lymphoma with 11q aberration (ICC)

WHO-HEAM5 changed the name of the Burkitt-like lymphoma with 11q aberration (WHO-HAEM4R) to High-grade B-cell lymphoma (HGBL) with 11q aberration, while it is large B-cell lymphoma with 11q aberration in the ICC. Those cases have morphological and pathological features (strikingly coarse apoptotic debris within starry sky macrophages)(76), phenotype, and gene expression profiles resembling those of Burkitt lymphoma (BL), but they are *MYC* rearrangements negative. Additionally, these lymphomas carry an 11q-arm aberration characterized by proximal gains and telomeric losses. (77)

Studies have revealed that HGBL-11q predominantly affects children and young individuals; however, it can also affect middle-aged and older persons. Irrespective of the age group, if patients have Burkitt-like morphology without MYC translocation, they should undergo FISH to detect 11q abnormalities. Pathophysiology, clinical features, and prognosis of HGBL-11q remain unknown (76, 78).

Potential driver mutations were found in 27 genes, including *BTG2*, *DDX3X*, *ETS1*, *EP300*, and *GNA13*. By contrast, the Burkitt lymphoma-associated *ID3*, *TCF3*, or *CCND3* mutations were absent in all cases. These results suggest that Burkitt-like lymphoma with 11q aberration is a germinal center-derived lymphoma closer to high-grade B-cell lymphoma or diffuse large B-cell lymphoma than to Burkitt lymphoma (77).

Large B-cell lymphoma with IRF4 rearrangement

Large B-cell lymphoma with *IRF4* rearrangement (LBCL-*IRF4*) is a rare B lymphoma subtype, usually occurring in the pediatric/young-adult age (79). It is often presented as a localized disease, typically involving cervical lymph nodes or Waldeyer ring. It is located under the umbrella of large B cell lymphomas and it is described as a distinct entity.

Fluid overload-associated large B-cell lymphoma (WHO-HEAM5)/HHV-8 and EBV-negative primary effusion-based lymphoma (ICC)

Fluid overload-associated large B-cell lymphoma is a type of rare effusion-based lymphoma that is related to fluid overflow but does not involve HHV-8. It is important to note that only cases with HHV-8 positivity can be classified as pleural effusion lymphomas (PEL), even though there may be some overlap with conventional PEL cases. Patients with large B-cell lymphomas usually have exclusive involvement of bodily cavities, most commonly the pleural cavity, and are usually elderly without underlying immunodeficiency. Fluid overload can be caused by various conditions, such as chronic heart failure, renal failure, protein-losing enteropathy, and liver cirrhosis (1, 2, 80). This entity has a good prognosis with spontaneous remission in some cases. The pathogenesis of the disease is related to chronic serosal inflammation (81, 82).

WHO- HEAM5 reports that cases may be associated with EBV; by contrast, ICC pointed out that the cases must be EBV negative (1, 2).

Fibrin-associated large B-cell lymphoma (WHO-HEAM5)/ Fibrin-associated large B-cell lymphoma (a subtype of DLBCL associated with chronic inflammation)(ICC)

Fibrin-associated large B-cell lymphoma (FA-LBL) is a new entity introduced by WHO-HEAM5, and previously considered a subtype of DLBCL, associated with chronic inflammation (1, 2, 83). According to the literature, FA-LBL is a rare subtype of lymphoma commonly identified as an incidental finding, usually without formation of mass lesion, associated chronic inflammatory conditions such as arterial aneurysm, cardiac or orthopedic prosthesis Rare cases of FA-DLBCL have been reported in association with another underlying neoplasm, such as atrial myxoma and ovarian cystic teratoma (84, 85) (86) (87). Cases usually present with GCB phenotype, EBV positivity, and usually carry a good prognosis (85).

In the case of a chronic inflammatory disease, FA-LBL is believed to be caused by a latent or long-lasting EBV infection. Normally, the immune system's cytotoxic T lymphocytes can identify and destroy B-cells infected with EBV and expressing LMP-1. The presence of foreign materials like metal implants or surgical mesh can lead to a persistent inflammatory environment, enrichd in immortalized EBV+ cells, from which a lymphoma may develop. EBV latent membrane protein-1 (LMP1) is believed to act as oncogenic factor by activating NF-kappa B and inducing BCL2 expression. These eventually prevent EBV-infected cells from undergoing apoptosis (85, 86, 88).

ICC continues to group FA-LBL under DLBCL associated with chronic inflammation (1, 2, 83).

Mediastinal Grey Zone Lymphoma

Mediastinal Grey zone Lymphoma (MGZL) is a new entity added by both WHO-HEAM-5 and ICC. It includes cases with overlapping pathologic criteria of both primary mediastinal B-cell lymphoma (PMBL) and Classical Hodgkin lymphoma (cHL) (often NS type), and replaced the entity “B-cell lymphoma, unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma” of WHO-HAEM4.

MGZL is thought to arise from a common precursor (e.g., thymic B-cell), which partly explains why cHL, PMBCL, or MGZL may relapse as one of the other related entities (89).

MGZL, in contrast to PMBL and cHL, is more common in young adult men and carries an aggressive clinical course and poorer outcome than either cHL or PMBL, so it is highly recommended to identify those cases as a specific entity for a better approach to therapy. It often presents with bulky mediastinal mass, and cases with extramediastinal involvement should be classified as DLBCL, NOS (89).

The diagnosis of MGZL is based on morphological and immunophenotypic criteria. About 70% of cases show a "cHL like morphology" resembling nodular sclerosis, with infrequent Hodgkin/Reed Sternberg cells surrounded by the typical cellular background (lymphocytes, eosinophils, histiocytes, plasma cells), and the rest mimic PMLBCL (monomorphic proliferation of medium-large neoplastic cells, inflammatory infiltrate). The neoplastic cells have strong expression of one or more B-cell markers (CD20, CD19, CD79A, CD79B), PAX5+ (strong), CD30+, while EBV is mostly negative (90). Cases expressing CD20 but testing negative for other B-cell markers, and having otherwise normal nodular sclerosis cHL, should not be classified as MGZL (1).

High-grade B Cell Lymphoma, NOS

High-grade B cell lymphoma, NOS remains a heterogeneous category with an aggressive nature, typically characterized by the presence of intermediate-size cells with GCB phenotype, often with blastoid or Burkitt-like morphology, but that cannot be classified as DLBCL or BL (91). Clinically, it affects older adults and it comes with high LDH, high IPI, extranodal involvement, CNS invasion, and a more aggressive behavior than DLBCL. Interestingly, gene expression profiling showed that 54% of HGBL, NOS harbour the "double hit" signature (DHITsig) characteristic of LBCL/HGBL with *MYC/BCL2* rearrangements despite lacking these specific genetic rearrangements. (91)

Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive lymphoma characterized by homogenous medium-sized cohesive neoplastic cells, with reticular chromatin and abundant nucleoli, basophilic cytoplasm, frequent "starry sky" pattern, GCB phenotype (CD10+, BCL6+,

BCL2−), high proliferative index (Ki67 > 95%), *IGH-MYC* juxtaposition and mutations involving *TCF3* or its repressor *ID3* (2).

WHO-HEAM5 recommended to sub-classify BL cases according to the EBV status rather than based on epidemiology, as in the past (2). This approach was suggested and supported by transcriptional and genetic evidence as well as functional studies (92-96). EBV makes B-cells capable of evading apoptosis (96), virus-driven cases are always associated with massive levels of somatic hypermutation typically in non-coding sequences (92) close to the transcription start site and carry a lower load of driver mutations, among which *TCF3* and *ID3* ones (97). It is currently believed that EBV might be essential for disease initiation. (96) Progressively, the viral genome can be lost to escape the immune system, due to dilution in highly proliferating neoplastic cells (cellular DNA replicates faster than episomal EBV DNA), and host genes mutations accumulate meanwhile. The main problem with the *hit-and-run* hypothesis is the lack of consistence evidence in primary tumors (98).

Despite the distinction between EBV+ and EBV- cases being absolutely relevant from the biological point of view, it should be still considered that cases arising in endemic areas present with additional specific features both as far as pathogenesis is concerned (eg. the role of malaria) and clinically (i.e. pediatric disease with peculiar clinical presentation).

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

Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8 (HHV8) was first discovered in an HIV-positive patient who also had acquired immunodeficiency syndrome and Kaposi sarcoma. (99) Both ICC and WHO-HEAM5 recognized a spectrum of lymphoid proliferations related to Kaposi sarcoma herpesvirus/human herpesvirus 8 (KSHV/ HHV8) infection, which include:

KSHV/HHV8-associated multicentric Castleman disease

KSHV/HHV8-associated multicentric Castleman disease is an aggressive inflammatory systemic disease that is different from classic lymphoma. The hallmarks of this disease include systemic

lymphadenopathy, cytopenia, hypoalbuminemia, hypergammaglobulinemia, splenomegaly, high serum C-reactive protein level, and constitutional symptoms. The proinflammatory state and clinical symptomatology of such patients are caused by high levels of IL-6. KSHV/HHV8-associated multicentric Castleman disease is more aggressive than idiopathic multicentric Castleman disease in terms of clinical manifestation. In patients with HIV, multicentric Castleman disease typically appears three years after the HIV diagnosis and is often associated with Kaposi sarcoma (100).

WHO-HEAM5 put multicentric Castleman disease under the new category of lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation and renamed it as KSHV/HHV8-associated multicentric Castleman disease (KSHV/HHV8-MCD). Differently, maintained the old nomenclature of the disease, not recognizing KSHV/HHV8-MCD as new category.

KSHV/HHV8-positive germinotropic lymphoproliferative disorder (WHO-HEAM5)/HHV8-positive germinotropic lymphoproliferative disorder (ICC)

KSHV/HHV8-positive germinotropic lymphoproliferative disorder is considered to be a rare disorder with limited cases in the literature, exhibiting localized lymphadenopathy in an asymptomatic and immunocompetent patient and carrying a good prognosis. The atypical cells, which show coinfection with EBV and HHV-8, have a propensity to grow within germinal centers (101).

Neoplastic cells are EBV+ but show negativity for LMP1, BNA2, and BZLF-1, indicating a latency type 1. They are also negative for PAX5, BCL6, CD10, CD20, CD79A, and CD30 (101).

WHO-HEAM5 changed the nomenclature of this category but ICC retained the former name.

KSHV/HHV8-positive diffuse large B-cell lymphoma (WHO-HEAM5)/ HHV8-positive diffuse large B-cell lymphoma, NOS (ICC)

KSHV/HHV8-positive diffuse large B-cell lymphoma typically occurs in individuals with HIV infection and multicentric Castleman disease. These tumors mainly affect lymph nodes, though they can also spread to other parts of the body and present with symptoms like splenomegaly and peripheral blood involvement. It is rare for these neoplasms to only affect

the spleen (102). The neoplastic cells are often positive for CD20, CD45, and terminal B-cell differentiation markers such as IRF4; conversely, they are always negative for CD79A, CD38, CD138 and EBER (103). They often lack somatic mutation of the *IGH* variable regions but have monoclonal *IGH* rearrangement (99).

Only WHO-HEAM5 and not ICC did chang the nomenclature of this category.

Primary effusion lymphoma

Primary effusion lymphoma (PEL) develops from HHV8-infected B-cells, which are often also infected with EBV. However, the majority of elderly HIV-negative individuals from HHV8 endemic locations are reported to have EBV-negative primary effusion lymphomas. (104) It is effusion-based, defined as a large B-cell lymphomatous growth in pleural, peritoneal, and/or pericardial effusion. (105) PEL is considered an AIDS-defining disease, typically occurs in middle-aged HIV-infected men with low CD4 counts, but it also can be found in patients with a broad range of $CD4^+$ T-cell counts and even in the setting of effective anti-viral therapy. The lymphoma cells usually express CD45 but lack pan-B-cell markers such as CD19, CD20, and CD79A.

Extracavity-Primary effusion lymphoma

Extracavity primary effusion lymphoma has the appearance, immunophenotype, and HHV8 viral status that match those of primary effusion lymphoma. Solid primary effusion lymphoma typically presents as extranodal tumors in the gastrointestinal tract, lung, central nervous system, or skin, with lymph node involvement being rare. Solid primary effusion lymphoma can be an initial, subsequent, or sole manifestation of cavity (classic) primary effusion lymphoma. Although most patients with primary effusion lymphoma have HIV, they often have less severe immunosuppression than those with solid primary effusion lymphoma. There have also been cases recorded in HIV-negative individuals. (99)

Hodgkin Lymphoma

Hodgkin lymphomas (HL) are lymphoid neoplasms in which malignant cells are mixed with a heterogeneous population of non-neoplastic inflammatory cells. Hodgkin lymphoma (HL) is divided into two major categories: classic HL and nodular lymphocyte-predominant HL.

Classical Hodgkin Lymphoma

Classical HL (cHL) comprises 90 percent of HL and is further subtyped according to pathologic features into four subtypes: nodular sclerosis cHL (NSCHL), mixed cellularity cHL (MCCHL), lymphocyte rich cHL (LRCHL), and lymphocyte depleted cHL (LDCHL).

The progression of cHL can vary, but it typically advances slowly. It is well-known that lymphadenopathy, exhaustion, constitutional symptoms, and/or pruritus may have started weeks or months before the patient is evaluated. Due to the slow pace of growth, mediastinal masses may become quite large before causing respiratory symptoms or chest discomfort.

At morphology, cHL presents with a typical, bizzarre morphological pattern that made impossible, til the advent of single cell PCR to unveil the lymphoid origin. Neoplastic cells can be scant (as few as 5% of the entire cellular population. They are named Reed-Sternberg (RS) cells and are typically large (more than 60mM) with two or more nuclei and evident nucleoli. The increased ploidy is thought to represent a failed caryorexis. The mononuclear variant is named Hodgkin (H) cell. H/RS cells are accompanied by reactive cells in the inflammatory tumor microenvironment, including T and B lymphocytes, eosinophils, plasma cells, and stromal cells. (34, 106)

The immunophenotype of HRS cells is typically characterized by CD30 expression, while CD15 is found in 75-85 percent of cases. (107) HRS cells do not express CD45 (leukocyte common antigen), which distinguishes them from normal leukocytes and most (but not all) other types of malignant lymphoma cells.

Additionally, HRS generally do not express CD20, CD79A, and/or CD19, which is characteristically either absent or may be seen in a rare subset of HRS cells. (108) PAX5 is

weakly expressed, whereas expression of other B cell-specific transcription factors (BOB1, OCT2) is typically lost in HRS cells (109). Aberrant expression of T-cell antigen may rarely occur as CD4 (110). HRS cells express PDL1 and PDL2, which are ligands for the PD1 immune checkpoint receptor, due to frequent amplification of chromosome 9p24.

Clonal immunoglobulin (*Ig*) gene rearrangements can be detected in more than 98 percent of cHL by polymerase chain reaction (PCR) on microdissected single HRS cells. (107). Indeed, this was used to demonstrate its lymphoid origin. The mutational landscape of cHL is heterogeneous, but most cases of cHL have abnormalities of intracellular signaling (eg, NF-kB or JAK-STAT pathways) and/or immune evasion. (111)

Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL)(WHO-HEAM5)/ Nodular Lymphocyte Predominant B-cell lymphoma (ICC)

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an unusual form of Hodgkin lymphoma with distinctive pathological and clinical characteristics. The lymphocyte-predominant cells formerly called L&H cells for lymphocytic and/or histiocytic Reed-Sternberg cell variants, that define the disease, are also called popcorn cells characterized by their single, large, folded, or multilobated nuclei. (112) Popcorn cells are embedded in enormous spherical meshworks of follicular dendritic cell processes containing non-malignant histiocytes and lymphocytes. These neoplastic cells typically show nodular infiltrate pattern and sometimes both nodular and diffuse infiltration. (34)

They are consistently positive for CD20 but do not express CD30, (113) unlike the malignant cells in cHL. NLPHL often affects middle-aged men and progresses slowly in most cases, with a tendency toward relapses and transformation into aggressive B-NHL; the majority of patients are diagnosed with early-stage illness. (114). Recent evidence indicated that NLPHL is likely to be a pathogen-driven disease, Moraxella catarrhalis being identified as a potential driver (115).

Based on a cellular biology and a clinical behavior much more similar to that of indolent B-NHL rather than cHL, ICC changed the term nodular lymphocyte predominant Hodgkin

lymphoma (NLPHL) into that of nodular lymphocyte predominant B-cell lymphoma. On the contrary, WHO-HAEM5 preferred to maintain the term NLPHL even though the editors recognized that NLPHL may be more accurately called "nodular lymphocyte predominant B-cell lymphoma" specially based on the presence of a functional B-cell program, and therefore there is a future direction toward changing the nomenclature.

Both ICC and WHO-HEAM5 emphasize the importance of identifying variant histology in NLPBL, as some variant patterns (patterns C, D, and E) have been associated with a more aggressive clinical course and may overlap with T-cell/histiocyte-rich large B-cell lymphoma. (116)

Plasma cell neoplasms and other diseases with paraproteins

Plasma cell neoplasms are a spectrum of neoplasms that range from asymptomatic monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) to symptomatic multiple myeloma (MM). (117) Clonal plasma cells secret M-proteins and cause a reduction in uninvolved immunoglobulins leading to immunoparesis (118). Diagnosis of these disorders requires the integration of clinical, laboratory, and morphological features. Overall, this chapter was largely modified by both WHO-HEMA5 and ICC, but with significant differences between the two.

IgM Monoclonal gammopathy of undetermined significance (MGUS)

IgM monoclonal gammopathy of unknown significance (MGUS) is distinguished from IgG or IgA MGUS by its characteristic progression to lymphoplasmacytic lymphoma (LPL) or other B-cell lymphoproliferative disorders, rather than multiple myeloma or other plasma cell neoplasms. (1, 119)

The diagnostic criteria of IgM monoclonal gammopathy of undetermined significance (MGUS) were not modified in the previous and both the current classifications. Diagnosis is made if less than 10% of BM cellularity is represented by neoplastic cells with lymphoplasmacytoid or plasma cell differentiation, without lymphoplasmacytic B-cell aggregates diagnostic of LPL.

On the other hand, the ICC describes two IgM MGUS entities: (1)

(1) The IgM MGUS of plasma cell type

This category belongs to a precursor of IgM-MM and it is characterized by the presence of clonal plasma-cells without B-cells and by the absence of *MYD88* mutation.

(2) The IgM MGUS, not otherwise specified (NOS)

This subtype refers to cases with the accumulation of monoclonal B cells (without lymphoplasmacytic aggregates) more often carrying mutations in *MYD88*. IgM MGUS/NOS may transform into LPL.

Cold Agglutinin Disease

Cold agglutinin disease (CAD) is an indolent bone marrow disorder characterized by autoimmune hemolytic anemia and production of a cold agglutinin monoclonal antibody of IgM type, caused by clonal B-cell proliferation that lacks the full diagnostic criteria to be diagnosed as B-cell lymphoma. CAD associated with nodal involvement or splenomegaly should be considered secondary CAD and should be excluded from this category. (120)

The clonal B-cells in primary CAD are light chain restricted with the expression of CD20, PAX5, CD79B, and FMC7 and they are negative for CD10, cyclin D1, and BCL6; they lack the *MYD88* L265P mutation. (121)

Primary CAD is recognized as a new diagnostic category in both ICC and WHO-HEAM5.

Monoclonal gammopathy of renal significance (MGRS)

Monoclonal gammopathy of renal significance (MGRS) is a heterogeneous series of kidney lesions (up to end-stage kidney disease) caused by a nephrotoxic monoclonal immunoglobulin produced by a clonal plasma cell or B-cell that does not meet current hematologic criteria for lymphoid neoplasm or multiple myeloma. It is usually diagnosed by kidney biopsy. Treatment decisions for MGRS should be made through collaboration between hematologists and nephrologists in a multidisciplinary approach. The focus should be on the identified

underlying clonal population. These decisions should be based on the type of MGRS, the extent of kidney function impairment, and the probability of progression to end-stage kidney disease.(122)

Monoclonal gammopathy of renal significance (MRGS) is a new entity introduced by WHO-HEAM5 but not ICC.

Plasma cell myeloma / Multiple Myeloma

Multiple myeloma (MM) is one of the prototypic plasma cell neoplasms, morphologically, phenotypically and functionally corresponding to terminally differentiated plasma cells (120). MM is diagnosed in patients fulfilling any of the SLiM-CRAB criteria according to the 2014 IMWG consensus.

MM is a very heterogeneous disease in terms of clinical behavior and at the genetic level with certain subtypes that exhibit specific clinical and/or biochemical characteristics. The majority of MM cases secrete a complete or incomplete monoclonal immunoglobulin (with IgG being the most common followed by light chains, IgA, IgM, IgD, and IgE). A very small percentage of patients lack detectable M-protein in the blood or urine, even when very sensitive tests like the free light chain ratio are performed, being defined non-secretory MM. Non-secretory MM patients do not experience M-protein-induced organ damage, such as renal failure, and have reduced levels of immunoparesis.(123)

According to ICC, MM can be divided into two diagnostic groups: (1) MM, NOS, and (2) MM with recurrent genetic abnormalities, including MM with CCND family translocations, MM with MAF family translocation, MM with *NSD2* translocation, and MM with hyperdiploidy. These subtypes are not included in the WHO-HEAM5 classification. The current standard for the detection of these cytogenetic aberrations is interphase fluorescence in situ hybridization (FISH). Detection of t(4;14), t(14;16), and secondary changes, including del(17p), amp1q, and del(1p) is highly recommended as it helps in better risk categorization of the patients for better therapeutic decisions. Additionally, The ICC committee preferred the

term MM rather than plasma cell myeloma while WHO-HEAM5 retain the two terms as reporting pathologists are often unaware of the extension of the disease.

Localized plasma cell neoplasms

Localized plasma cell neoplasms include two entities (83):

- Solitary Plasmacytoma of the bone
- Primary extraosseous/extramedullary plasmacytoma (EMP)

They are characterized by masses of clonal plasma cells with the absence of manifest bone marrow infiltration, even if minimal bone marrow involvement can be detected by immunophenotyping as less than 10% clonal plasma cells. The ICC strongly emphasizes determining the state of minimal BM infiltration into the diagnosis and using flow cytometry for staging in every localized plasma cell neoplasms as it carries strong prognostic factors regarding the future probability of transformation to overt MM (120).

Plasma cell neoplasms with associated paraneoplastic syndrome

TEMPI syndrome is characterized by telangiectasia, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting. It is an acquired disorder with a vague pathogenesis, maybe the monoclonal protein triggers a paraneoplastic syndrome leading to over overproduction of EPO production. (124) The bone marrow examination is unremarkable in the majority of cases; a few cases show erythroid hyperplasia (2). It is now considered a distinct entity by WHO-HEAM5 but not in ICC.

AESOP syndrome (adenopathy and extensive skin patch overlying a plasmacytoma) is a rare plasma neoplasm characterized by the presence of a gradually expanding erythematous skin patch that overlies a bone-associated plasmacytoma, accompanied by locoregional lymphadenopathy first described

in 2003 by Lipsker et al.(125, 126). Skin biopsies of patients with AESOP syndrome show diffuse hyperplasia of dermal vessels associated with dermal mucin, and lymph nodes can show some features of Castleman disease (127). AESOP syndrome is now considered a distinct entity in WHO-HEAM5 but not in ICC.

Disease with monoclonal immunoglobulin deposition

There is a change in the nomenclature of some entities as the primary amyloidosis in WHO-HEAM4R is now renamed as immunoglobulin-related (AL) amyloidosis by WHO-HEAM5 and Ig light chain amyloidosis (AL) by ICC. Additionally, light chain and heavy chain deposition disease was renamed as monoclonal immunoglobulin deposition disease by WHO.

Moreover, ICC recommended the separation of localized AL amyloidosis (also termed “amyloid tumor”) which is, a rare disorder with an excellent prognosis and rare progression to systemic AL amyloidosis as a distinct entity.

Conclusion

The two novel classification schemes presented in 2022 showed some striking changes to the nomenclature, definition, and entities of mature B cell neoplasm, and significant differences between each other. To ensure consistency and clarity, there is an urgent need for a common language and unifying the two classifications to be used worldwide. The aim is a better classification and characterization of hematolymphoid neoplasm serving as a key for precision medicine and better decision-making processes for patients' good.

Declarations

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Conflict of Interest

The Authors declare that there is no conflict of interest.

Table 1.

Table 1. Mature B-cell neoplasms according to WHO-HEMA5 and ICC

WHO-HEMA5	ICC
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	Same
Chronic lymphocytic Leukemia/small lymphocytic lymphoma	Same
-	B-cell prolymphocytic leukemia
Splenic B-cell lymphomas and Leukemias	
Hairy cell Leukemia	

Splenic marginal zone lymphoma Splenic diffuse red pulp small B-cell lymphoma Splenic B-cell lymphoma/Leukemia with prominent nucleoli	*Splenic B-cell lymphoma/leukemia, unclassifiable* • *Splenic diffuse red pulp small B-cell lymphoma* • *Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma	Same
Marginal zone lymphoma	Same
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	Primary cutaneous marginal zone disorder
Primary cutaneous marginal zone lymphoma	Same
Nodal marginal zone lymphoma	*Perdiatric nodal marginal zone lymphoma*
Paediatric marginal zone lymphoma	
Follicular lymphoma	In situ follicular neoplasia
In situ follicular B-cell neoplasm	Same
Follicular lymphoma	Same
Paediatric-type follicular lymphoma	Same
Duodenal-type follicular lymphoma	Primary cutaneous follicle center lymphoma
Cutaneous follicle centre lymphoma	*BCL2-R–negative, CD23-positive follicle center lymphoma*
	Testicular follicular lymphoma
Mantle cell lymphoma	In situ mantle cell neoplasia
In situ mantle cell neoplasm	Same
Mantle cell lymphoma	Same
Leukemic non-nodal mantle cell lymphoma	-
Transformations of indolent B-cell lymphomas	Diffuse large B-cell lymphoma, NOS • Germinal center B-cell subtype • Activated B-cell subtype
Large B-cell lymphomas	

Diffuse large B-cell lymphoma, NOS	Same
	High-grade B-cell lymphoma, with MYC and BCL2 rearrangements*
	High-grade B-cell lymphoma with MYC and BCL6
T-cell/histiocyte-rich large B-cell lymphoma	*rearrangements**
Diffuse large B-cell lymphoma/ high grade	Same
B-cell lymphoma with *MYC* and *BCL2* rearrangements	Same
	Same
	Same
	EBV-positive diffuse large B-cell
ALK-positive large B-cell lymphoma	lymphoma, NOS
Large B-cell lymphoma with *IRF4* rearrangement	Same
High-grade B-cell lymphoma with 11q aberrations	Same (but under DLBCL associated with chronic inflammation)
Lymphomatoid granulomatosis	-
EBV-positive diffuse large B-cell lymphoma	Same
	Primary DLBCL of testis
Diffuse large B-cell lymphoma associated with chronic inflammation	Same
Fibrin-associated large B-cell lymphoma	
	Same
Fluid overload-associated large B-cell lymphoma	Same
	Same
Plasmablastic lymphoma	Same
Primary large B-cell lymphoma of immune-privileged sites	Same
Primary cutaneous diffuse large B-cell lymphoma, leg type	**HHV-8–associated lymphoproliferative disorders**
Intravascular large B-cell lymphoma	
Primary mediastinal large B-cell lymphoma	Same
Mediastinal grey zone lymphoma	HHV-8–positive diffuse large B-cell
High-grade B-cell lymphoma, NOS	lymphoma, NOS
	HHV-8–positive germinotropic
Burkitt lymphoma	lymphoproliferative disorder

	Multicentric Castleman disease
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas Primary effusion lymphoma KSHV/HHV8-positive diffuse large B-cell lymphoma KSHV/HHV8-positive germinotropic lymphoproliferative disorder	**Immunodeficiency-associated lymphoproliferative disorders** - Polymorphic posttransplant lymphoproliferative disorder Same (not under this chapter)

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
Hyperplasias arising in immune deficiency/dysregulation
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation
EBV-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency
Inborn error of immunity-associated lymphoid proliferations and lymphomas
	Posttransplant lymphoproliferative disorders
	• Nondestructive posttransplant lymphoproliferative disorders
	  ○ Plasmacytic hyperplasia posttransplant lymphoproliferative disorder
	  ○ Infectious mononucleosis posttransplant lymphoproliferative disorder
	  ○ Florid follicular hyperplasia posttransplant lymphoproliferative disorder
	• Monomorphic posttransplant lymphoproliferative disorder (B-cell and T-cell/NK-cell types)†
	• Classic Hodgkin lymphoma posttransplant lymphoproliferative disorder†
	Other iatrogenic immunodeficiency-associated lymphoproliferative disorders
	Same

	Nodular lymphocyte predominant B-cell lymphoma
Hodgkin lymphoma	
Classic Hodgkin lymphoma	
Nodular lymphocyte predominant Hodgkin lymphoma	
	Primary cold agglutinin disease
	Immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS)
Plasma cell neoplasms and other diseases with paraproteins	- IgM MGUS, plasma cell type
Monoclonal gammopathies	- IgM MGUS, not otherwise specified (NOS)
Cold agglutinin disease	
IgM monoclonal gammopathy of undetermined significance	Non-IgM MGUS
	-
Non-IgM monoclonal gammopathy of undetermined significance	
Monoclonal gammopathy of renal significance Not previously included	**Monoclonal Ig deposition diseases**
	Ig light chain amyloidosis (AL)
Diseases with monoclonal immunoglobulin deposition	Localized AL amyloidosis
Immunoglobulin-related (AL) amyloidosis	Light chain and heavy chain deposition disease
-	Same
Monoclonal immunoglobulin deposition disease	Same
Heavy chain diseases	Same
Mu heavy chain disease	Same
Gamma heavy chain disease	
Alpha heavy chain disease	Solitary plasmacytoma of bone + Extraosseous plasmacytoma
	Multiple myeloma (plasma cell myeloma)
Plasma cell neoplasms	- Multiple myeloma, NOS
Plasmacytoma	

Plasma cell myeloma	- Multiple myeloma with recurrent genetic abnormality - Multiple myeloma with *CCND* family translocation - Multiple myeloma with *MAF* family translocation - Multiple myeloma with *NSD2* translocation - Multiple myeloma with hyperdiploidy
Plasma cell neoplasms with associated paraneoplastic syndrome -POEMS syndrome -TEMPI syndrome -AESOP syndrome	-
	Italic indicates provisional entities † Further classified according to the lymphoma to which they correspond

References

1. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. Blood, The Journal of the American Society of Hematology. 2022;140(11):1229-53. doi.org/10.1182/blood.2022015851

2. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBdO, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720-48. doi.org/10.1038/s41375-022-01620-2

3. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka H-M, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood, The Journal of the American Society of Hematology. 2022;140(11):1200-28. doi.org/10.1182/blood.2022015850

4. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-19. doi.org/10.1038/s41375-022-01613-1

5. Lenz G, Staudt LM. Aggressive lymphomas. New England Journal of Medicine. 2010;362(15):1417-29. doi:10.1056/NEJMra0807082
6. Piccaluga PP, Khattab SS. A Comparison of the Fifth World Health Organization and the International Consensus Classifications of Mature T-Cell Lymphomas. International Journal of Molecular Sciences. 2023;24(18):14170. **doi.org/10.3390/ijms241814170**
7. Marti GE, Rawstron AC, Ghia P, Hillmen P, Houlston RS, Kay N, et al. Diagnostic criteria for monoclonal B-cell lymphocytosis. British journal of haematology. 2005;130(3):325-32. **doi.org/10.1111/j.1365-2141.2005.05550.x**
8. Rawstron AC, Shanafelt T, Lanasa MC, Landgren O, Hanson C, Orfao A, et al. Different biology and clinical outcome according to the absolute numbers of clonal B-cells in monoclonal B-cell lymphocytosis (MBL). Cytometry Part B: Clinical Cytometry. 2010;78(S1):S19-S23. **doi.org/10.1002/cyto.b.20533**
9. Xochelli A, Oscier D, Stamatopoulos K. Clonal B-cell lymphocytosis of marginal zone origin. Best Practice & Research Clinical Haematology. 2017;30(1-2):77-83. **doi.org/10.1016/j.beha.2016.08.028**
10. Jain P, Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. American journal of hematology. 2019;94(6):710-25. **doi.org/10.1002/ajh.25487**
11. Oishi N, Montes-Moreno S, Feldman AL, editors. In situ neoplasia in lymph node pathology. Seminars in Diagnostic Pathology; 2018: Elsevier. doi.org/10.1053/j.semdp.2017.11.001
12. Carvajal-Cuenca A, Sua LF, Silva NM, Pittaluga S, Royo C, Song JY, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. Haematologica. 2012;97(2):270. doi: 10.3324/haematol.2011.052621
13. Hsu P, Yang T, Sheikh-Fayyaz S, Brody J, Bandovic J, Roy S, et al. Mantle cell lymphoma with in situ or mantle zone growth pattern: a study of five cases and review of literature. International journal of clinical and experimental pathology. 2014;7(3):1042.
14. Rawstron AC, Kreuzer KA, Soosapilla A, Spacek M, Stehlikova O, Gambell P, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. Cytometry Part B: Clinical Cytometry. 2018;94(1):121-8. **doi.org/10.1002/cyto.b.21595**
15. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood, The Journal of the American Society of Hematology. 2018;131(25):2745-60. doi.org/10.1182/blood-2017-09-806398
16. Zent CS, Burack WR. Mutations in chronic lymphocytic leukemia and how they affect therapy choice: focus on NOTCH1, SF3B1, and TP53. Hematology 2014, the American Society of Hematology Education Program Book. 2014;2014(1):119-24. doi.org/10.1182/asheducation-2014.1.119
17. Rasi S, Khiabanian H, Ciardullo C, Terzi-di-Bergamo L, Monti S, Spina V, et al. Clinical impact of small subclones harboring NOTCH1, SF3B1 or BIRC3 mutations in chronic lymphocytic leukemia. Haematologica. 2016;101(4):e135. doi: 10.3324/haematol.2015.136051

18. Cortese D, Sutton LA, Cahill N, Smedby K, Geisler C, Gunnarsson R, et al. On the way towards a 'CLL prognostic index': focus on TP53, BIRC3, SF3B1, NOTCH1 and MYD88 in a population-based cohort. Leukemia. 2014;28(3):710-3. doi:10.1038/leu.2013.333
19. Hampel PJ, Ding W, Call TG, Rabe KG, Kenderian SS, Witzig TE, et al. Rapid disease progression following discontinuation of ibrutinib in patients with chronic lymphocytic leukemia treated in routine clinical practice. Leukemia & lymphoma. 2019;60(11):2712-9. doi.org/10.1080/10428194.2019.1602268
20. Tadmor T, Levy I. Richter transformation in chronic lymphocytic leukemia: update in the era of novel agents. Cancers. 2021;13(20):5141. **doi.org/10.3390/cancers13205141**
21. Condoluci A, Rossi D. Richter syndrome. Current oncology reports. 2021;23:1-10. doi.org/10.1007/s11912-020-01001-x
22. Yamamoto JF, Goodman MT. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997–2002. Cancer Causes & Control. 2008;19:379-90. DOI 10.1007/s10552-007-9097-2
23. Wang A, Guo W, Damiani D, Sumbly V, Goyal G, Du Z, et al. B-cell prolymphocytic leukemia with P53 abnormalities successfully treated with bendamustine and rituximab: a report of three cases. Translational Cancer Research. 2023;12(7):1873. doi: 10.21037/tcr-23-828
24. Dearden C. How I treat prolymphocytic leukemia. Blood, The Journal of the American Society of Hematology. 2012;120(3):538-51. doi.org/10.1182/blood-2012-01-380139
25. Matutes E, Morilla R, Owusu-Ankomah K, Houliham A, Meeus P, Catovsky D. The immunophenotype of hairy cell leukemia (HCL). Proposal for a scoring system to distinguish HCL from B-cell disorders with hairy or villous lymphocytes. Leukemia & lymphoma. 1994;14:57-61.
26. Troussard X, Maître E, Cornet E. Hairy cell leukemia 2022: Update on diagnosis, risk-stratification, and treatment. American Journal of Hematology. 2022;97(2):226-36. **doi.org/10.1002/ajh.26390**
27. Perrone S, D'Elia GM, Annechini G, Ferretti A, Tosti ME, Foà R, et al. Splenic marginal zone lymphoma: prognostic factors, role of watch and wait policy, and other therapeutic approaches in the rituximab era. Leukemia research. 2016;44:53-60. doi.org/10.1016/j.leukres.2016.03.005
28. Donzel M, Baseggio L, Fontaine J, Pesce F, Ghesquières H, Bachy E, et al. New insights into the biology and diagnosis of splenic marginal zone lymphomas. Current Oncology. 2021;28(5):3430-47. **doi.org/10.3390/curroncol28050297**
29. Gautam A, Sreedharanunni S, Sachdeva MUS, Rana S, Kashyap D, Bose P, et al. The relative expression levels of CD148 and CD180 on clonal B cells and CD148/CD180 median fluorescence intensity ratios are useful in the characterization of mature B cell lymphoid neoplasms infiltrating blood and bone marrow–Results from a single centre pilot study. International Journal of Laboratory Hematology. 2021;43(5):1123-31. **doi.org/10.1111/ijlh.13467**
30. Mayeur-Rousse C, Guy J, Miguet L, Bouyer S, Geneviève F, Robillard N, et al. CD 180 expression in B-cell lymphomas: A multicenter GEIL study. Cytometry Part B: Clinical Cytometry. 2016;90(5):462-6. **doi.org/10.1002/cyto.b.21325**
31. Watkins AJ, Hamoudi RA, Zeng N, Yan Q, Huang Y, Liu H, et al. An integrated genomic and expression analysis of 7q deletion in splenic marginal zone lymphoma. 2012. doi.org/10.1371/journal.pone.0044997
32. Bertoni F, Rossi D, Zucca E. Recent advances in understanding the biology of marginal zone lymphoma. F1000Research. 2018;7. doi: 10.12688/f1000research.13826.1

33. Yan Q, Huang Y, Watkins AJ, Kocialkowski S, Zeng N, Hamoudi RA, et al. BCR and TLR signaling pathways are recurrently targeted by genetic changes in splenic marginal zone lymphomas. haematologica. 2012;97(4):595. doi: 10.3324/haematol.2011.054080
34. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues: International agency for research on cancer Lyon, France; 2008.
35. Yilmaz E, Chhina A, Nava VE, Aggarwal A. A review on splenic diffuse red pulp small B-cell lymphoma. Current Oncology. 2021;28(6):5148-54. **doi.org/10.3390/curroncol28060431**
36. Curiel-Olmo S, Mondéjar R, Almaraz C, Mollejo M, Cereceda L, Marès R, et al. Splenic diffuse red pulp small B-cell lymphoma displays increased expression of cyclin D3 and recurrent CCND3 mutations. Blood, The Journal of the American Society of Hematology. 2017;129(8):1042-5. doi.org/10.1182/blood-2016-11-751024
37. Rai V, Saha A, Gondha S, Manimaran P, Sawhney J. Splenic B-cell lymphoma/leukemia with prominent nucleoli: A three-case series of the newly named old entity and review of literature. Journal of Cancer Research and Therapeutics. 2023. *DOI:* 10.4103/jcrt.jcrt_1931_22
38. Tran J, Gaulin C, Tallman MS. Advances in the treatment of hairy cell leukemia variant. Current treatment options in oncology. 2022;23(1):99-116. DOI 10.1007/s11864-021-00927-z
39. Wang W, Lin P. Lymphoplasmacytic lymphoma and Waldenström macroglobulinaemia: clinicopathological features and differential diagnosis. Pathology. 2020;52(1):6-14. doi.org/10.1016/j.pathol.2019.09.009
40. Treon S, Hunter Z, Aggarwal A, Ewen E, Masota S, Lee C, et al. Characterization of familial Waldenström's macroglobulinemia. Annals of Oncology. 2006;17(3):488-94. doi.org/10.1093/annonc/mdj111
41. Pozzato G, Mazzaro C, Crovatto M, Modolo ML, Ceselli S, Mazzi G, et al. Low-grade malignant lymphoma, hepatitis C virus infection, and mixed cryoglobulinemia. 1994. doi.org/10.1182/blood.V84.9.3047.3047
42. Konoplev S, Medeiros LJ, Bueso-Ramos CE, Jorgensen JL, Lin P. Immunophenotypic profile of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia. American journal of clinical pathology. 2005;124(3):414-20. doi.org/10.1309/3G1XDX0DVHBNVKB4
43. Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. New England Journal of Medicine. 2012;367(9):826-33. DOI: 10.1056/NEJMoa1200710
44. Treon SP, Xu L, Guerrera ML, Jimenez C, Hunter ZR, Liu X, et al. Genomic landscape of Waldenström macroglobulinemia and its impact on treatment strategies. Journal of Clinical Oncology. 2020;38(11):1198. doi: 10.1200/JCO.19.02314
45. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood, The Journal of the American Society of Hematology. 2016;127(17):2082-92. doi.org/10.1182/blood-2015-12-624304
46. Cheah CY, Zucca E, Rossi D, Habermann TM. Marginal zone lymphoma: present status and future perspectives. Haematologica. 2022;107(1):35. doi: 10.3324/haematol.2021.278755
47. Zucca E, Raderer M. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Indolent Lymphomas. 2021:93-115. doi.org/10.1007/978-3-030-55989-2
48. Falini B, Tiacci E, Pucciarini A, Bigerna B, Kurth J, Hatzivassiliou G, et al. Expression of the IRTA1 receptor identifies intraepithelial and subepithelial marginal zone B cells of the mucosa-

associated lymphoid tissue (MALT). Blood. 2003;102(10):3684-92. doi.org/10.1182/blood-2003-03-0750
49. Spina V, Khiabanian H, Messina M, Monti S, Cascione L, Bruscaggin A, et al. The genetics of nodal marginal zone lymphoma. Blood, The Journal of the American Society of Hematology. 2016;128(10):1362-73. doi.org/10.1182/blood-2016-02-696757
50. Knauf W, Abenhardt W, Koenigsmann M, Maintz C, Sandner R, Zahn MO, et al. Rare lymphomas in routine practice–Treatment and outcome in marginal zone lymphoma in the prospective German Tumour Registry Lymphatic Neoplasms. Hematological Oncology. 2021;39(3):313-25. **doi.org/10.1002/hon.2868**
51. Thieblemont C, Molina T, Davi F. Optimizing therapy for nodal marginal zone lymphoma. Blood, The Journal of the American Society of Hematology. 2016;127(17):2064-71. doi.org/10.1182/blood-2015-12-624296
52. Koo M, Ohgami RS. Pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma: recent clinical, morphologic, immunophenotypic, and genetic insights. Advances in Anatomic Pathology. 2017;24(3):128-35. doi.org/10.1097/PAP.0000000000000144
53. Gitelson E, Al-Saleem T, Robu V, Millenson MM, Smith MR. Pediatric nodal marginal zone lymphoma may develop in the adult population. Leukemia & lymphoma. 2010;51(1):89-94. doi.org/10.3109/10428190903349670
54. Tadmor T, Polliack A. Nodal marginal zone lymphoma: clinical features, diagnosis, management and treatment. Best Practice & Research Clinical Haematology. 2017;30(1-2):92-8. doi.org/10.1016/j.beha.2016.08.026
55. O'Suoji C, Welch JJ, Perkins SL, Smith LM, Weitzman S, Simko SJ, et al. Rare pediatric non-Hodgkin lymphomas: a report from Children's Oncology Group study ANHL 04B1. Pediatric Blood & Cancer. 2016;63(5):794-800. **doi.org/10.1002/pbc.25881**
56. Gibson SE, Swerdlow SH. How I diagnose primary cutaneous marginal zone lymphoma. American Journal of Clinical Pathology. 2020;154(4):428-49. doi.org/10.1093/ajcp/aqaa116
57. Oertel M, Khaled E, Carsten W, Kerstin S, Eich HT. De-escalated radiotherapy for indolent primary cutaneous B-cell lymphoma. Strahlentherapie Und Onkologie. 2020;196(2):126-31. DOI:10.1007/s00066-019-01541-7
58. Vitiello P, Sica A, Ronchi A, Caccavale S, Franco R, Argenziano G. Primary cutaneous B-cell lymphomas: an update. Frontiers in Oncology. 2020;10:651. doi.org/10.3389/fonc.2020.00651
59. Edinger JT, Kant JA, Swerdlow SH. Cutaneous marginal zone lymphomas have distinctive features and include 2 subsets. The American journal of surgical pathology. 2010;34(12):1830-41. *DOI:* 10.1097/PAS.0b013e3181f72835
60. Piccaluga PP, Califano A, Klein U, Agostinelli C, Bellosillo B, Gimeno E, et al. Gene expression analysis provides a potential rationale for revising the histological grading of follicular lymphomas. Haematologica. 2008;93(7):1033-8. doi.org/10.3324/haematol.12754
61. Etebari M, Gatua M, Navari M, Piccaluga PP, Kaggia S, Rogena E, et al. Molecular Detection of BCL2/IGH Rearrangement in Follicular Lymphoma in Low Resource Settings-A Phase III Diagnostic Accuracy Study. Biomedical Journal of Scientific & Technical Research. 2021;39(3):31439-42. DOI: 10.26717/BJSTR.2021.39.006318
62. Carbone A, Roulland S, Gloghini A, Younes A, von Keudell G, López-Guillermo A, et al. Follicular lymphoma. Nature reviews Disease primers. 2019;5(1):83. doi.org/10.1038/s41572-019-0132-x

63. Cree IA, Tan PH, Travis WD, Wesseling P, Yagi Y, White VA, et al. Counting mitoses: SI (ze) matters! Modern Pathology. 2021;34(9):1651-7. doi.org/10.1038/s41379-021-00825-7
64. Metter GE, Nathwani BN, Burke JS, Winberg CD, Mann RB, Barcos M, et al. Morphological subclassification of follicular lymphoma: variability of diagnoses among hematopathologists, a collaborative study between the Repository Center and Pathology Panel for Lymphoma Clinical Studies. Journal of Clinical Oncology. 1985;3(1):25-38. doi.org/10.1200/JCO.1985.3.1.25
65. Piccaluga PP, Pileri SA, Agostinelli C, Klapper W, Lennert K. Follicular lymphoma: still Six characters in search of an author? Leukemia & Lymphoma. 2011;52(9):1655-67. doi.org/10.3109/10428194.2011.575493
66. Hershkovitz-Rokah O, Pulver D, Lenz G, Shpilberg O. Ibrutinib resistance in mantle cell lymphoma: clinical, molecular and treatment aspects. British journal of haematology. 2018;181(3):306-19. **doi.org/10.1111/bjh.15108**
67. Saba NS, Liu D, Herman SE, Underbayev C, Tian X, Behrend D, et al. Pathogenic role of B-cell receptor signaling and canonical NF-κB activation in mantle cell lymphoma. Blood, The Journal of the American Society of Hematology. 2016;128(1):82-92. . doi.org/10.1182/blood-2015-11-681460
68. Royo C, Navarro A, Clot G, Salaverria I, Giné E, Jares P, et al. Non-nodal type of mantle cell lymphoma is a specific biological and clinical subgroup of the disease. Leukemia. 2012;26(8):1895-8. doi:10.1038/leu.2012.72
69. Navarro A, Clot G, Royo C, Jares P, Hadzidimitriou A, Agathangelidis A, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer research. 2012;72(20):5307-16. https://doi.org/10.1158/0008-5472.CAN-12-1615
70. Xu J, Wang L, Li J, Saksena A, Wang SA, Shen J, et al. SOX11-negative Mantle Cell Lymphoma. The American Journal of Surgical Pathology. 2019;43(5):710-6. doi.org/10.1097/PAS.0000000000001233
71. Falini B, Martino G, Lazzi S. A comparison of the International Consensus and 5th World Health Organization classifications of mature B-cell lymphomas. Leukemia. 2023;37(1):18-34. doi.org/10.1038/s41375-022-01764-1
72. Kledus F, Filip D, Mráz M. Transformation of indolent follicular lymphoma into diffuse large B-cell lymphoma-the molecular basis of" cancer aggressiveness". Klinicka Onkologie: Casopis Ceske a Slovenske Onkologicke Spolecnosti. 2023;36(4):353-63. doi.org/10.48095/ccko2023353
73. Zerbini MCN, Soares FA, Velloso EDRP, Paes RP. World Health Organization Classification of tumors of hematopoietic and lymphoid tissues, 2008–major changes from the 3rd edition, 2001. Revista da Associação Médica Brasileira (English Edition). 2011;57(1):66-73. doi.org/10.1016/S2255-4823(11)70019-4
74. Pasqualucci L, Dalla-Favera R. Genetics of diffuse large B-cell lymphoma. Blood. 2018;131(21):2307-19. doi.org/10.1182/blood-2017-11-764332
75. Reddy A, Zhang J, Davis NS, Moffitt AB, Love CL, Waldrop A, et al. Genetic and functional drivers of diffuse large B cell lymphoma. Cell. 2017;171(2):481-94. e15. doi.org/10.1016/j.cell.2017.09.027
76. Horn H, Kalmbach S, Wagener R, Staiger AM, Hüttl K, Mottok A, et al. A diagnostic approach to the identification of Burkitt-like lymphoma with 11q aberration in aggressive B-cell lymphomas. The American journal of surgical pathology. 2021;45(3):356-64. doi.org/10.1097/PAS.0000000000001613

77. Salaverria I, Martin-Guerrero I, Wagener R, Kreuz M, Kohler CW, Richter J, et al. A recurrent 11q aberration pattern characterizes a subset of MYC-negative high-grade B-cell lymphomas resembling Burkitt lymphoma. Blood, The Journal of the American Society of Hematology. 2014;123(8):1187-98. doi.org/10.1182/blood-2013-06-507996
78. Yamada S, Oka Y, Muramatsu M, Hashimoto Y. High-grade B-cell lymphoma with 11q aberrations: A single-center study. Journal of clinical and experimental hematopathology. 2023;63(2):121-31. doi.org/10.3960/jslrt.23007
79. Pizzi M, Bongiovanni L, Lorenzi L, Righi S, Scarmozzino F, Balzarini P, et al. Large B-cell lymphoma with IRF4 rearrangement: a multi-centric study with focus on potential misleading phenotypes. Virchows Archiv. 2023:1-6. doi.org/10.1007/s00428-023-03689-1
80. Song JY, Dirnhofer S, Piris MA, Quintanilla-Martínez L, Pileri S, Campo E. Diffuse large B-cell lymphomas, not otherwise specified, and emerging entities. Virchows Archiv. 2023;482(1):179-92. doi.org/10.1007/s00428-022-03466-6
81. Gisriel SD, Yuan J, Braunberger RC, Maracaja DL, Chen X, Wu X, et al. Human herpesvirus 8-negative effusion-based large B-cell lymphoma: a distinct entity with unique clinicopathologic characteristics. Modern Pathology. 2022;35(10):1411-22. doi.org/10.1038/s41379-022-01091-x
82. Kaji D, Ota Y, Sato Y, Nagafuji K, Ueda Y, Okamoto M, et al. Primary human herpesvirus 8–negative effusion-based lymphoma: a large B-cell lymphoma with favorable prognosis. Blood Advances. 2020;4(18):4442-50. doi.org/10.1182/bloodadvances.2020002293
83. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, The Journal of the American Society of Hematology. 2016;127(20):2375-90. doi.org/10.1182/blood-2016-01-643569
84. Boyer DF, McKelvie PA, De Leval L, Edlefsen KL, Ko Y-H, Aberman ZA, et al. Fibrin-associated EBV-positive large B-cell lymphoma. The American journal of surgical pathology. 2017;41(3):299-312. doi.org/10.1097/PAS.0000000000000775
85. Chu W, Zhang B, Zhang Y, Tian D, Tang Y, Zhang W, et al. Fibrin-associate diffuse large B-Cell lymphoma arising in a left atrial myxoma: A case report and literature review☆,☆☆. Cardiovascular Pathology. 2020;49:107264. doi.org/10.1016/j.carpath.2020.107264
86. Loong F, Chan AC, Ho BC, Chau Y-P, Lee H-Y, Cheuk W, et al. Diffuse large B-cell lymphoma associated with chronic inflammation as an incidental finding and new clinical scenarios. Modern Pathology. 2010;23(4):493-501. doi.org/10.1038/modpathol.2009.168
87. Maedeh M, Francisco T, Sunny K, Craig O, Jessica D, Guang F. Recurrent fibrin associated diffuse large B-cell lymphoma: a case report. Human Pathology: Case Reports. 2021;25:200538. doi.org/10.1016/j.ehpc.2021.200538
88. Boroumand N, Ly TL, Sonstein J, Medeiros LJ. Microscopic diffuse large B-cell lymphoma (DLBCL) occurring in pseudocysts: do these tumors belong to the category of DLBCL associated with chronic inflammation? The American Journal of Surgical Pathology. 2012;36(7):1074-80. *DOI:* 10.1097/PAS.0b013e3182515fb5
89. Quintanilla-Martinez L, Fend F. Mediastinal gray zone lymphoma. haematologica. 2011;96(4):496. doi: 10.3324/haematol.2011.043026
90. Wilson WH, Pittaluga S, Nicolae A, Camphausen K, Shovlin M, Steinberg SM, et al. A prospective study of mediastinal gray-zone lymphoma. Blood, The Journal of the American Society of Hematology. 2014;124(10):1563-9. doi.org/10.1182/blood-2014-03-564906

91. Collinge B, Hilton L, Wong J, Ben-Neriah S, Rushton C, Slack G, et al. Characterization of the genetic landscape of high-grade b-cell lymphoma, nos–An llmpp project. Hematological Oncology. 2021;39. **doi.org/10.1002/hon.13_2880**
92. Bellan C, Lazzi S, Hummel M, Palummo N, de Santi M, Amato T, et al. Immunoglobulin gene analysis reveals 2 distinct cells of origin for EBV-positive and EBV-negative Burkitt lymphomas. Blood. 2005;106(3):1031-6. doi.org/10.1182/blood-2005-01-0168
93. Piccaluga PP, De Falco G, Kustagi M, Gazzola A, Agostinelli C, Tripodo C, et al. Gene expression analysis uncovers similarity and differences among Burkitt lymphoma subtypes. Blood, The Journal of the American Society of Hematology. 2011;117(13):3596-608. doi.org/10.1182/blood-2010-08-301556
94. Abate F, Ambrosio MR, Mundo L, Laginestra MA, Fuligni F, Rossi M, et al. Distinct viral and mutational spectrum of endemic Burkitt lymphoma. PLoS pathogens. 2015;11(10):e1005158. doi.org/10.1371/journal.ppat.1005158
95. Navari M, Etebari M, Ibrahimi M, Leoncini L, Piccaluga PP. Pathobiologic roles of Epstein–Barr virus-encoded MicroRNAs in human lymphomas. International journal of molecular sciences. 2018;19(4):1168. **doi.org/10.3390/ijms19041168**
96. Piccaluga PP, Navari M, De Falco G, Ambrosio MR, Lazzi S, Fuligni F, et al. Virus-encoded microRNA contributes to the molecular profile of EBV-positive Burkitt lymphomas. Oncotarget. 2016;7(1):224. doi: 10.18632/oncotarget.4399
97. Grande BM, Gerhard DS, Jiang A, Griner NB, Abramson JS, Alexander TB, et al. Genome-wide discovery of somatic coding and noncoding mutations in pediatric endemic and sporadic Burkitt lymphoma. Blood, The Journal of the American Society of Hematology. 2019;133(12):1313-24. doi.org/10.1182/blood-2018-09-871418
98. Mundo L, Ambrosio MR, Picciolini M, Lo Bello G, Gazaneo S, Del Porro L, et al. Unveiling another missing piece in EBV-driven lymphomagenesis: EBV-encoded microRNAs expression in EBER-negative Burkitt lymphoma cases. Frontiers in Microbiology. 2017;8:229. doi.org/10.3389/fmicb.2017.00229
99. Vega F, Miranda RN, Medeiros LJ. KSHV/HHV8-positive large B-cell lymphomas and associated diseases: a heterogeneous group of lymphoproliferative processes with significant clinicopathological overlap. Modern pathology. 2020;33(1):18-28. doi.org/10.1038/s41379-019-0365-y
100. Oksenhendler E, Boutboul D, Fajgenbaum D, Mirouse A, Fieschi C, Malphettes M, et al. The full spectrum of Castleman disease: 273 patients studied over 20 years. British Journal of Haematology. 2018;180(2):206-16. **doi.org/10.1111/bjh.15019**
101. Bhavsar T, Lee JC, Perner Y, Raffeld M, Xi L, Pittaluga S, et al. KSHV-associated and EBV-associated Germinotropic Lymphoproliferative Disorder: New Findings and Review of the Literature. Am J Surg Pathol. 2017;41(6):795-800. 10.1097/PAS.0000000000000823
102. Dupin N, Diss TL, Kellam P, Tulliez M, Du M-Q, Sicard D, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8–positive plasmablastic lymphoma. Blood, The Journal of the American Society of Hematology. 2000;95(4):1406-12. doi.org/10.1182/blood.V95.4.1406.004k26_1406_1412
103. Chadburn A, Said J, Gratzinger D, Chan JK, de Jong D, Jaffe ES, et al. HHV8/KSHV-positive lymphoproliferative disorders and the spectrum of plasmablastic and plasma cell neoplasms: 2015

SH/EAHP workshop report—part 3. American Journal of Clinical Pathology. 2017;147(2):171-87. doi.org/10.1093/ajcp/aqw218
104. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood, The Journal of the American Society of Hematology. 2012;120(20):4150-9. doi.org/10.1182/blood-2012-04-421412
105. Simonelli C, Spina M, Cinelli R, Talamini R, Tedeschi R, Gloghini A, et al. Clinical features and outcome of primary effusion lymphoma in HIV-infected patients: a single-institution study. Journal of Clinical Oncology. 2003;21(21):3948-54. DOI: 10.1200/JCO.2003.06.013
106. Mottok A, Steidl C. Biology of classical Hodgkin lymphoma: implications for prognosis and novel therapies. Blood, The Journal of the American Society of Hematology. 2018;131(15):1654-65. doi.org/10.1182/blood-2017-09-772632
107. Gobbi PG, Cavalli C, Gendarini A, Crema A, Ricevuti G, Federico M, et al. Reevaluation of prognostic significance of symptoms in Hodgkin's disease. Cancer. 1985;56(12):2874-80. **doi.org/10.1002/1097-0142(19851215)56:12<2874::AID-CNCR2820561227>3.0.CO;2-2**
108. Schmid C, Pan L, Diss T, Isaacson PG. Expression of B-cell antigens by Hodgkin's and Reed-Sternberg cells. Am J Pathol. 1991;139(4):701-7.
109. Schmitz R, Stanelle J, Hansmann ML, Küppers R. Pathogenesis of classical and lymphocyte-predominant Hodgkin lymphoma. Annu Rev Pathol. 2009;4:151-74. doi: 10.1146/annurev.pathol.4.110807.092209
110. Venkataraman G, Song JY, Tzankov A, Dirnhofer S, Heinze G, Kohl M, et al. Aberrant T-cell antigen expression in classical Hodgkin lymphoma is associated with decreased event-free survival and overall survival. Blood. 2013;121(10):1795-804. doi.org/10.1182/blood-2012-06-439455
111. Spina V, Bruscaggin A, Cuccaro A, Martini M, Di Trani M, Forestieri G, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. Blood. 2018;131(22):2413-25. doi.org/10.1182/blood-2017-11-812073
112. Mason DY, Banks PM, Chan J, Cleary ML, Delsol G, de Wolf Peeters C, et al. Nodular lymphocyte predominance Hodgkin's disease: A distinct clinicopathological entity. LWW; 1994. p. 526-30.
113. Eichenauer DA, Engert A. How I treat nodular lymphocyte-predominant Hodgkin lymphoma. Blood, The Journal of the American Society of Hematology. 2020;136(26):2987-93. doi.org/10.1182/blood.2019004044
114. Lee AI, LaCasce AS. Nodular lymphocyte predominant Hodgkin lymphoma. The oncologist. 2009;14(7):739-51. doi.org/10.1634/theoncologist.2009-0099
115. Thurner L, Fadle N, Regitz E, Roth S, Cetin O, Kos IA, et al. B-cell receptor reactivity against Rothia mucilaginosa in nodular lymphocyte-predominant Hodgkin lymphoma. Haematologica. 2020. doi: 10.3324/haematol.2023.282698
116. Hartmann S, Eichenauer DA, Plütschow A, Mottok A, Bob R, Koch K, et al. The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG). Blood, The Journal of the American Society of Hematology. 2013;122(26):4246-52. doi.org/10.1182/blood-2013-07-515825
117. Gupta L, Suku P, Dash A, Bose P, Sharma P, Mallik N, et al. Detection of circulating normal and tumor plasma cells in newly diagnosed patients of multiple myeloma and their associations with clinical and laboratory parameters. Current Problems in Cancer. 2024;48:101025. doi.org/10.1016/j.currproblcancer.2023.101025Get rights and content

118. Sarı M, Sarı S, Nalcacı M. The effect of suppressed levels of uninvolved immunoglobulins on the prognosis of symptomatic multiple myeloma. Turkish Journal of Hematology. 2017;34(2):131. DOI: 10.4274/tjh.2016.0161
119. Bruehl FK, Mannion P, Barbato E, Nakashima MO, Cook JR. IgM monoclonal gammopathy of undetermined significance: clinicopathologic features with and without IgM-related disorders. Haematologica. 2023;108(10):2764. doi: 10.3324/haematol.2022.282389
120. Fend F, Dogan A, Cook JR. Plasma cell neoplasms and related entities—evolution in diagnosis and classification. Virchows Archiv. 2023;482(1):163-77. doi.org/10.1007/s00428-022-03431-3
121. Agbuduwe C, Iqbal G, Cairns D, Menzies T, Dunn J, Gregory W, et al. Clinical characteristics and outcomes of IgD myeloma: experience across UK national trials. Blood Advances. 2022;6(17):5113-23. doi.org/10.1182/bloodadvances.2022007608
122. Karam S, Haidous M, Abou Dalle I, Dendooven A, Moukalled N, Van Craenenbroeck A, et al. Monoclonal Gammopathy of Renal Significance: multidisciplinary approach to diagnosis and treatment. Critical Reviews in Oncology/Hematology. 2023:103926. doi.org/10.1016/j.critrevonc.2023.103926
123. Dupuis MM, Tuchman SA. Non-secretory multiple myeloma: from biology to clinical management. OncoTargets and therapy. 2016:7583-90. doi.org/10.2147/OTT.S122241
124. Landsman A, Barua P, Podrumar A. A Rare Coexistence of Multiple Myeloma and Polycythemia Vera. Journal of Hematology. 2023;12(5):227. DOI:10.14740/jh1167
125. Yan W, Lv R, Xu J, Li L, Cui J, Liu Y, et al. Adenopathy and extensive skin patch overlying a plasmacytoma (AESOP) syndrome: a case report and literature review. Annals of Hematology. 2023:1-3. doi.org/10.1007/s00277-023-05465-2
126. Lipsker D, Rondeau M, Massard G, Grosshans E. The AESOP (adenopathy and extensive skin patch overlying a plasmacytoma) syndrome: report of 4 cases of a new syndrome revealing POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome at a curable stage. Medicine. 2003;82(1):51-9.
127. Farooq U, Choudhary S, McLeod MP, Torchia D, Rongioletti F, Romanelli P. Adenopathy and extensive skin patch overlying a plasmacytoma (AESOP) syndrome. The Journal of Clinical and Aesthetic Dermatology. 2012;5(11):25.