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Lymphoma classification

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Abstract

Twenty-five years after the Revised European American Lymphoma (REAL) classification was published, its principle of an integrative approach to disease definition based on several parameters still prevails and has been adopted and expanded in the following World Health Organization (WHO) classifications of tumors of the haematopoietic organs. The latest WHO classification revised in 2017 comprises more than 80 entities of mature lymphoid neoplasms (B-cell, T-cell and Hodgkin lymphomas) which are defined according to their morphology, immunophenotype, genetic lesions and molecular profiles, clinical features and cellular derivation. The classification also recognizes both incipient and indolent lymphoid neoplasms with a low potential of proegression. In this review we highlight some of the new data and recent modifications introduced in the 2017 classification.

Keywords

Lymphoma – classification – Hodgkin – gray zone – indolent – cutaneous – digestive – WHO

A historical perspective of lymphoma classification

Few areas in pathology have evoked as much controversy and confusion as the classification of lymphoid neoplasms, dating back to the first attempts to organize the variety of described neoplasms into a comprehensive scheme. The difficulties resulted from several factors, notably the diversity of lymphoid tumors, and the relative insensitivity of routine histopathological techniques that are useful in other organ systems in recognizing defining features of lymphoid cells and their tumors. Later on, in parallel with advances in immunology and genetics, and with the development of novel technologies, the past decades have witnessed major advances in the knowledge of lymphoma pathology, biology and genetics, which translated to novel concepts for the classification of lymphoma (**Figure 1**)[1,2].

Before 1970, several purely morphologically oriented descriptive classifications of lymphomas were proposed [3-6]. The **Rappaport proposal** (1966) was the first clinically relevant classification[6]. Broadly speaking, Rappaport divided lymphomas into those composed of small cells and of large cells, and further subdivided according to follicular (or nodular) *versus* diffuse growth patterns. The follicular and small-cell tumors were clinically less aggressive; a better survival could therefore be expected and, importantly, less potent and less toxic therapy was suitable for these cases. The converse applied to cases with a diffuse growth pattern, especially if composed of large cells.

Immunologic advances in the 1960's and 1970's revolutionized the understanding of the immune system and lymphomas. The existence of several lymphoid lineages was discovered, and it became possible to establish the phenotype of lymphoma cells using monoclonal antibodies and immunolabeling techniques. Soon it became evident that the lymphoma cells were closely related to normal lymph node cells and that the cells of the non-Hodgkin lymphomas recapitulated the cytology of normal lymphocytes, particularly the B cells of the follicle center. Several new schemes based on these new concepts appeared. The **Kiel Classification**[7,8] developed by Karl Lennert in Germany became widely used in Europe; in this approach primarily intended for classification of nodal diseases, lymphomas were classified according to a hypothetical scheme of B- and T-lymphocyte differentiation, and the nomenclature reflected the putative normal counterpart of the neoplastic cells. According to their cytological characteristics rather than their predetermined clinical behavior and in keeping with established schemes for other tumors, the lymphomas were designated low-grade and high-grade. The classification developed by Lukes and Collins (1974) in the United States was based on similar concepts[9], and several other proposals appeared shortly after.

Because of the multiplicity of classifications causing much confusion, the compromise **« Working Formulation for Clinical Use »** (NHL Classification Project, 1982) was developed and designed to « translate » between the various classifications[10]. In this scheme, non-Hodgkin lymphomas were divided on clinical grounds into three prognostic groups: low, intermediate and high-grade. Within each group, classification was based purely on morphologic criteria, in particular the nodular versus diffuse growth pattern and the size of the tumor cells (small *versus* large *versus* mixed small and large). As a result, different clinico-pathological entities were lumped together and the Working Formulation did not incorporate immunophenotypic data. In the 1980's and early 1990's, the Working Formulation became the standard American[11] classification, while the Kiel classification was most widely used in Europe. This lack of consensus on lymphoma classification and terminology caused problems for both pathologists and clinicians, and caused difficulty in interpreting published studies. In addition, in the 1980's and 1990's, many new disease entities were described, for example mantle cell lymphoma[12] and

extranodal marginal zone lymphoma[13], which were not included in either classification. At the same time there were tremendous advances in the understanding of the genetic basis of B-cell lymphomas with the successive discovery of several recurrent translocations and protooncogenes (*BCL2, MYC, CCND1*) [14,15]. The progresses made in immunogenetics with the descriptions of the process of gene rearrangement of immunoglobulin and T-cell receptor genes in normal lymphocytes, and of somatic hypermutations occurring in immunoglobulin genes during transit through the germinal center, were soon exploited to infer clonality and lineage derivation of lymphoid neoplasms, and differentiation stage of B-cell neoplasms [11,16]. Ultimately, the introduction of the new techniques of immunophenotyping and molecular genetic analysis led to confusion about what, if anything, should be the modern "gold standard" for defining disease entities.

In 1991, Peter Isaacson and Harald Stein founded the International Lymphoma Study Group (ILSG) to promote a better communication between hematopathologists from Europe and America. The group composed of 19 prominent hematopathologists from the United States, Europe and Asia at that time, aimed at defining "real" disease entities on which they could reach a consensus based on published data. This approach represented a new paradigm in lymphoma definition and classification. A consensus list of well-defined disease entities was published in 1994 as the **REAL (Revised European-American Classification of Lymphoid Neoplasms)** classification[1]. Some entities were listed as provisional due to insufficient knowledge or evidence for establishing them as definitive. In the REAL classification, distinct lymphomas defined by a constellation of five properties, namely morphology, immunophenotype, genetic features, clinical features, and if possible the normal cell counterpart from which they derive. The degree to which these properties contribute to the classification of each disease entity is variable. The integration of clinical features into lymphoma definition, which is particularly important for T-cell and NK-cell lymphomas, was a very innovative aspect of the REAL classification. Later on, the notion that the site of lymphoma presentation could represent a signpost for important underlying biologic distinctions was later reflected in the delineation of several "organ-specific" lymphoma entities, notably specific extranodal entities of diffuse large B-cell lymphomas (primary mediastinal, leg-type, of the central nervous system) or follicular lymphomas (cutaneous, duodenal-type, testicular). Although the initial publication of the REAL classification elicited considerable controversy[17], experience over the following years showed that it could be reproducibly applied by most pathologists and that the entities described have distinctive clinical features, making it a useful and practical classification[18,19].

Shortly after the publication of the REAL classification, the World Health Organization (WHO) commissioned the European and American Societies of Hematopathology, to provide an update of the classification of hematopoietic and lymphoid neoplasms for its "blue book" series. In addition to many hematopathologists, the joined project which took several years also involved a large clinical advisory committee to address questions of clinical relevance. The principles of disease definition and consensus developed in the REAL classification were essentially maintained. The **WHO classification** of lymphomas published at the end of 2001 [2] represented the first true international consensus on the classification of hematologic malignancies, and gained acceptance worldwide as the reference for pathologists, clinicians, scientists and researchers. Significantly, the monograph belonged to a new series of blue books entitled "pathology and genetics of cancer" emphasizing the contribution of genetics to tumor classification. Since 2001, the WHO classification of tumors of hematopoietic and lymphoid tissues was updated in 2008[20] and the latter edition was revised in 2017[21]. While the original principles still prevail the successive editions have been expanded to incorporate new knowledge and emphasize

novel concepts resulting in an increasing number of entities and amount of information. In the last edition, the "genetic profile" sections are in general markedly enlarged and comprise a lot of new data derived from the many next-generation sequencing studies performed over the past few years, including molecular signatures, (epi)genetic profiles, mutational landscapes and new fusion genes, which mechanistically may correspond to translocations, intrachromosomal deletions or inversions. The genomic landscapes of the most common non-Hodgkin lymphoma entities show wide heterogeneity within and across subtypes, but there are also similar altered pathways and mechanisms of oncogenesis overlapping across different entities.[22]. Various genes belonging to multiple functional pathways are mutated, and the pattern of mutations for each gene is variable: some genes like *BRAF* or *MYD88* are characterized by one or a few hotspot alterations[23,24], or the mutations may be more heterogeneous. Sometimes distinct mutations in the same gene may be either activating or loss-of-function, and mutations with apparently discordant functional impact may be encountered in different cases of the same disease[25]. Some disease entities are associated to a very characteristic mutational profile, involving one or a few genes, while other diseases are genetically more heterogeneous [26].

The WHO classification of lymphoid neoplasms

In the 2017 classification, more than 80 mature lymphoma entities are recognized, grouped into three major categories: B-cell neoplasms, T-cell and NK-cell neoplasms, and Hodgkin lymphomas (**Table 1**). Both lymphomas and lymphoid leukemias are included in this classification. The disease entities are listed according to predominant clinical presentation (predominantly disseminated diseases that often involve bone marrow and may be leukemic, primary extranodal lymphomas, and predominantly nodal diseases - which are often disseminated and may also involve extranodal sites -). There is an additional section on immunodeficiency-associated lymphoproliferative disorders addressing the spectrum of lymphoproliferations and lymphomas associated with primary immune deficiencies, HIV infection, in the post-transplant setting or in other iatrogenic conditions.

Following the principles of lymphoma classification, lymphoma diagnosis is based on the appreciation of morphologic and immunophenotypic features, genetic characteristics, in the context of clinical presentation. Assignement to a disease category requires the integration of these pieces of data for a final interpretation. In practice, morphologic interpretation combined to immunophenotyping represent the essential elements and are sufficient to establish the diagnosis in many cases. Technical factors in the preparation of the lymph node specimens are of critical importance for obtaining high-quality conventional histologic preparations, which are the essential starting point for accurate diagnosis[27]. In principle the immunologic or molecular studies should always be interpreted in the light of the clinical and histopathogical features. Immunophenotype is an essential defining characteristic of lymphomas. In the assessment of malignant lymphoproliferations, immunophenotyping is used (1) to determine cell lineage and differentiation stage, (2) to infer clonality from immunoglobulin light chain expression in the case of B-cell lymphoproliferations, and (3) to identify markers of specific genetic alterations. Immunoglobulin and T-cell receptor gene rearrangement studies are useful to characterize the clonality status of lymphoproliferations, results should again always be interpreted with caution as there are many examples of clonal proliferations that may remain subclinical or indolent. Moreover, pseudoclonal results may be generated from small biopsies with limited infiltrates and PCR amplification of a limited repertoire. Molecular or genetic testing is mandatory to assign a diagnostic category in some instances, for example FISH studies searching for *MYC, BCL2* or *BCL6* gene

rearrangements are necessary for the categorization of high-grade B-cell neoplasms[28]. Next generation sequencing technology has also entered the diagnostic arena, and can provide complementary information to support diagnoses[29].

B-cell lymphomas

Mature B-cell neoplasms comprise over 80% of NHL. The most common types are follicular lymphoma and diffuse large B-cell lymphoma, which together account for more than half of all NHL. B-NHL entities comprise a range of morphologically, phenotypically, genetically and clinically distinct malignancies. The majority of B-NHL harbor somatically mutated IG genes and therefore are derived from germinal center (GC) or post-GC B cells. The correspondence to normal B-cell subpopulations initially assessed by a combination of morphology and immunophenotype, has been refined by the comparison of gene expression signatures of lymphomas and normal B cell subpopulations across the full range of normal B-cell differentiation. **Figure 2** illustrates the model of histogenesis and pathogenesis of B-cell neoplasms.

Several entities of B-cell neoplasms represent early or indolent clonal lymphoid lesions. Monoclonal B-cell lymphocytosis and monoclonal gammopathy of unknow significance are the subclinical precursor lesions to B-chronic lymphocytic leukemia and plasma cell myeloma, respectively [30]. *In situ* follicular neoplasia (not uncommon) and *in situ* mantle cell lymphoma (distinctively rare) denote tissue accumulation restricted to germinal centers of mantle zones, of B cells harboring the *BCL2* or *CCND1* hallmark translocations of follicular or mantle cell lymphoma[31]. *In situ* follicular neoplasia is considered the tissue equivalent of circulating blood cells harboring the t(14;18) translocation found in many healthy individuals; compared to clinically overt follicular lymphoma the load of additional genetic alterations is low in *in situ* follicular neoplasia[32], and the risk of progression to clinical disease is low[33]. Duodenal-type follicular-type is somewhat assimilated to *in situ* follicular neoplasia, because this t(14;18)+ neoplasm which arises in the mucosa of the proximal duodenum is often discovered incidentally and has an indolent course with a very low risk of local progression or dissemination[34].

Major changes have been introduced in the classification and diagnosis of aggressive B-cell lymphomas, which fall into three main categories: diffuse large B-cell lymphomas (DLBCLs), Burkitt lymphoma (BL), and two novel entities of high-grade B-cell lymphomas[35]. DLBCLs constitutes the most prevalent group and comprises many entities unified by a simple definition, i.e. a proliferation of large transformed B cells. Specific entities are related to occurrence in peculiar anatomic sites (primary mediastinal, primary cutaneous leg-type, primary DLBCL of the central nervous system, intravascular), some are classified based on a plasmablastic phenotype (plasmablastic lymphoma and ALK-positive DLBCL) or an abundant microenvironment (T-cell/histiocyte-tich large B-cell lymphoma), others are defined by their association to viral infections +/- a peculiar clinical context (EBV+ DLBCL, EBV+ muco-cutaneous ulcer, DLBCL with chronic inflammation, lymphomatoid granulomatosis, primary effusion lymphoma, HHV8+ DLBCL-NOS). For the usual form of DLBCL ("NOS") it is recommended to identify the two molecular subtypes defined by gene expression profiling, germinal center-like and activated B-cell like, because these two subtypes correspond to distinct pathogenetic pathways. In a routine setting, this is achieved in most centers by the use of immunohistochemical algorithms or simplified RNA profiling methods[36-39]. Besides Burkitt lymphoma which is a very homogeneous category, a new provisional entity named Burkitt-like lymphoma with 11q aberration has been introduced, referring to a limited number of cases resembling Burkitt lymphoma, but lacking a *MYC*

translocation, having more complex karyotypes and a chromosome 11q aberration[40]. The categories of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, and high-grade B-cell lymphoma, not otherwise specified, were newly introduced. These new categories partly substitute for the former group of "unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma", which is no longer recognized. High-grade B-cell lymphomas may morphologically resemble DLBCL, have features intermediate between DLBCL and Burkitt lymphoma (high proliferation fraction and a starry sky appearance with cells larger or more pleomorphic than the spectrum of classical Burkitt lymphoma, or a morphology resembling Burkitt lymphoma with a discordant immunophenotype, typically strong BCL2 expression), or have a blastoid morphology. A sizeable fraction of high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements, also simply termed « double hit » or « triple hit » lymphomas, represent transformed follicular lymphomas. *MYC* plus *BCL2* double hit lymphomas are usually GCB and those with *MYC* and *BCL6* rearrangement are usually ABC. High-grade B-cell lymphomas NOS by definition do not have double or triple hits, but a significant proportion carries a *MYC* rearrangement (alone). An important consequence of this new classification is that assignement of a large B-cell neoplasm to the DLBCL category requires genetic testing at least for *MYC* +/- *BCL2* and *BCL6* rearrangements, in order to exclude the possibility of a "double hit" lymphoma.

T-cell lymphomas

Neoplasms of mature NK or T cells (PTCLs) are overall rare. They comprise approximately 10% of all lymphomas in Western world, while in Asia where EBV-associated extranodal NK/T-cell lymphoma (and adult T-cell leukemia/lymphoma) are more frequent, they represent up to 20% of lymphomas. The delineation of mature NK/T-cell neoplasms into entities along the WHO scheme is not as sharp as for the B-cell tumors, in regard to the numerous T-cell subsets and their functional plasticity. Indeed many T/NK-cell neoplasms have a broad range of cellular composition, and immunophenotypic profiles may be heterogeneous within a disease category while overlapping across different entities. Recent advances in characterizing the molecular profiles and mutational landscapes of these diseases have translated into significant changes in the classification.

With regard to nodal PTCLs (**Figure 3**), a major change was the grouping of angioimmunoblastic T-cell lymphoma and two related entities, namely follicular T-cell lymphoma and nodal T-cell lymphoma with a T follicular helper phenotype, under a common heading named "nodal lymphomas derived from follicular helper T cells (TFH cells). The rationale is that these three entities have in common not only an immunophenotype and gene expression signature similar to those normal TFH cells, but also a similar genetic landscape, characterized by recurrent mutations in epigenetic modifier genes (*TET2, DNMT3A, IDH2*), *RHOA* and other T-cell receptor signaling genes [41-48]. Nodal T-cell lymphoma with a T follicular helper phenotype is defined as a PTCL lacking the peculiar morphological features characteristic of AITL, but showing expression of several (at least two, optimally at least three) TFH markers, and this entitiy includes many cases categorized in the past as "Lennert lymphomas" (rich in epithelioid cells) or nodal T-zone lymphomas. Anaplastic large cell lymphoma (ALCL), ALK-negative, is now viewed as a genetically heterogeneous entity comprising at least two subsets defined by recurrent translocations affecting *DUSP22* (about 30% of the cases, and associated to a good prognosis similar to that of ALK-positive ALCL) or *TP63* (10% of the cases, associated with a poor outcome) [49,50]. Since *DUSP22*-rearranged cases may not fulfill all the phenotypic attributes of

ALK-negative ALCL, their identification is important to clarify the sometimes difficult differential diagnosis with CD30-positive PTCL-NOS. In addition, a proportion of ALK- ALCL also carry mutations impacting on the JAK/STAT pathway[51], a feature also reported in primary cutaneous ALCL[51] and breast implant-associated ALCL [52-54]. The latter was introduced as a provisional entity in the classification due to its peculiar clinical presentation usually as an effusion and less commonly as a tumor mass around a breast implant, and in the light of its peculiar epidemiology and usually indolent clinical course[55,56]. PTCL-NOS remains a diagnosis of exclusion - notably implying the exclusion of a TFH expression - and a heterogeneous category. Two molecular subtypes based on gene expression profiles related to Th1 or TH2 subsets of helper T cells, have been defined and can be identified by a surrogate immunohistochemistry-based algorithm[57,58]. A small subset of primary nodal PTCL-NOS are associated to EBV infection of the neoplastic cells; these cases differ from extranodal NK/T-cell lymphoma, nasal type as they tend to be more monomorphic, usually lack angioinvasion and necrosis, and do not express CD56[59].

Hodgkin lymphomas and gray zone lymphomas

Hodgkin lymphomas (HLs)differ from most other lymphomas in their unique cellular composition comprising a minority of large atypical neoplastic cells (Hodgkin and Reed-Sternberg (HRS) cells and their variants) outnumbered by non-neoplastic reactive cells[60]. After decades of uncertainties and speculations regarding the nature of this malignancy, genetic molecular studies conducted on microdissected HRS cells established that HLs are neoplasms of large B cells and represent clonal populations of transformed germinal center B cells [61-66]. Remarkably, however, the historical distinction between Hodgkin's disease and non-Hodgkin lymphomas survived the successive classifications of lymphomas over time - reflecting not only the peculiar morphological range of HL but also its distinctive clinical presenting features and distinctive responses to certain chemotherapeutic combinations and radiation therapy.

Classic HLs (cHLs) and nodular lymphocyte predominant HL (NLPHL) represent two distinctive groups of diseases (**Table 2**). In cHL subclassified into four subtypes according to the cellular composition of the background infiltrate, the neoplastic Hodgkin and Reed-Sternberg (HRS) which may harbor the Epstein-Barr virus (EBV) cells are typically positive for CD30 (an activation marker) and for CD15 (an antigen associated with the granulocyte and monocyte lineages), while they usually lack expression of CD45 and of molecules characteristic of the B and T-cell lineages[67]. In contrast, in NLPHL, the neoplastic LP "popcorn" cells, have a B-cell immunophenotype [68], and in its classical form develop within large follicular structures[69]. Six distinct histological patterns of NLPHL (A to F) have been recognized[70]and should be described in the diagnosis since the "non-classical" patterns (C to F) tend to correlate with higher disease stage and a higher risk of relapse[71]. There are clinical similarities and some morphologic overlap between the lymphocyte-rich subtype of cHL and NLPHL, which explains a high rate of misdiagnoses in the past[72]. However, despite the facts that the neoplastic cells in lymphocyte-rich cHL tend to have preserved expression of B-cell markers and develop in a follicular microenvironment rich in PD1-positive cells, similar to NLPHL [73]the two entities are separated by other key distinctive features.

The term "gray-zone lymphomas" was coined to denote lymphoproliferations rich in large cells and difficult to classify due to morphological or immunophenotypic overlapping features between

Hodgkin and non-Hodgkin lymphomas, suggesting the possibility of a biological overlap or continuum[74]. Some of the differential diagnoses considered under the "gray-zone" umbrella, in particular anaplastic large cell lymphoma versus cHL, have been resolved with the refinement of diagnostic criteria and the use of expanded immunohistochemistry and molecular genetic testing. Currently, there remains essentially two gray zone areas, one each around cHL and NLPHL.

The category of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and cHL, which was a provisional entity in the 2008 classification, was promoted to a definitive status in 2017. This entity mostly applies mostly to mediastinal cases showing both overlapping features between nodular sclerosis HL and primary mediastinal large B-cell lymphoma, and significant discordances between morphology and immunophenotype preventing from allocating the case to one of each of the well-defined entities[75]. The patients who are often young males, tend to experience a clinical course more aggressive than those with either Hodgkin or large B-cell lymphoma[76]. The notion of a biological continuum is supported by the partial overlap in the molecular and genetic features of mediastinal cHL, large B-cell lymphoma and gray-zone cases[77-79]. Recent studies have highlighted considerable variability among pathologists towards the diagnosis of mediastinal gray zone lymphomas, and the lack of consensus criteria[79,80]. EBV-positive cases should be excluded from the gray zone category as it turns out that these cases are either syncytial forms of EBV-positive nodular sclerosis HL, or part of the spectrum of EBV-positive diffuse large B-cell lymphomas.

The relationship and borderline between NLPHL and T-cell/histiocyte-rich large B-cell lymphoma has been addressed abundantly in the literature and remains a matter of debate[81]. The diffuse pattern of NLPHL which is often T-cell-rich, closely resembles de novo T-cell/histiocyte-rich large B-cell lymphoma not only on morphological grounds, but also at the transcriptional and genomic levels, with common recurrent mutations in *DUSP2*, *JUNB*, *SGK1* and *SOCS1*, and tends to follow a somewhat aggressive course[82,83]. However, it is recommended in the WHO classification to restrict the diagnosis of T-cell/histiocyte-rich large B-cell lymphoma to de novo cases, and to employ the term "T-cell/histiocyte-rich large B-cell lymphoma-like transformation" in cases progressing from NLPHL or arising in association with the classical nodular pattern of NLPHL [21].

Lymphomas of the digestive system

Lymphomas involving the gastrointestinal (GI) tract account for about 30 to 40% of extranodal lymphomas [84,85]. Most cases correspond to entities that are not specific to the GI tract, and a smaller fraction correspond to few specific tumor entities primarily arising in the gastrointestinal tract, including duodenal-type follicular lymphoma and intestinal T-cell lymphomas. The latest classification introduced significant changes in the intestinal T-cell lymphoma comprises four categories: enteropathy-associated T-cell lymphoma (EATL), formerly type I EATL and linked to celiac disease and frequent in Northern Europe; monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly type II EATL, not associated to celiac disease and relatively more frequent in Asia; intestinal T-cell lymphoma NOS, and indolent T-cell lymphoproliferative disorder of the GI tract[21]. The two subtypes of EATL previously considered as variants of the same disease, have been reclassified as two distinct diseases (**Figure 4**) due to differences in their epidemiology and clinical, features, morphology and phenotype, and genetic features as highlighted in recent works[56,86,87]. Intestinal T-cell lymphoma NOS is a category created to comprise the cases of primary intestinal T-cell lymphomas not meeting the criteria for either EATL or MEITL. Indolent T-cell lymphoproliferative disorder of the GI tract represent a novel category of clonal

monomorphic proliferations of small T cells showing a superficial/mucosal distribution in the colon or anywhere along the GI tract, usually characterized by an indolent behavior and a chronic relapsing course[88,89]. Recent works have demonstrated an association with recurrent gene fusions or point mutations[90,91]. All the recent updates of the 2017 lymphoma classification are also included in a specific section of the blue book on digestive system tumours dedicated to hematolymphoid malignancies[92].

Cutaneous lymphomas

Primary cutaneous lymphomas represent the second most common form of extranodal lymphomas. They comprise a heterogenous group of lymphomas that present in the skin without extracutaneous disease at the time of diagnosis. Primary cutaneous T-cell lymphomas represent the vast majority of the cases while B-cell lymphomas account for 20-25% primary cutaneous lymphomas. Several primary cutaneous lymphoma entities like mycosis fungoides or lymphomatoid papulosis, have highly characteristic clinical and histological features; conversely some lymphomas histologically similar to systemic lymphomas like follicular lymphoma or diffuse large B-cell lymphomas, often have a completely different clinical behavior and prognosis when occurring primarily in the skin. Because of these specificities, primary cutaneous lymphomas have been considered separately from systemic lymphomas in different classification systems. The consensus classification of the WHO-EORTC (World health Organization -European Organization for Research and Treatment of Cancer) published the first time in 2005 and recently revised, serves as the reference for the classification and diagnosis of primary cutaneous lymphomas[93,94]. The approach and principles for disease definition and diagnosis are similar to those used for systemic lymphomas, with increased contribution of genetic and molecular markers in the last edition, but perhaps more importantly than for systemic lymphomas, it must be stressed that clinical data remain essential for a correct diagnosis. For the most part, the terminology and defining criteria of the different primary cutaneous lymphoma entities of the updated WHO-EORTC classification were already introduced in the 2017 WHO classification of tumors of haematopoietic tissues[21]. The latest edition of the WHO blue book on skin tumors published in 2018[95], also incorporates the revised WHO-EORTC classification more completely with regards to the distinction of two different subtypes of cutaneous marginal zone lymphomas, one class-switched and comprising a small proportion of neoplastic B cells that are CXCR3-negative, and the other characterized by large nodules of neoplastic cells that are IgM- and CXCR3-positive[96-98].

Table 1

2017 WHO classification of mature lymphomas (adapted from [21])

B-cell Neoplasms

Predominantly disseminated

- Chronic lymphocytic leukemia/ B-cell small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis,
- B-cell prolymphocytic leukemia
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Splenic B-cell lymphoma/leukemia, unclassifiable*
- Splenic diffuse red pulp small B-cell lymphoma*
- Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Monoclonal gammopathy of unknown significance (MGUS) IgM
- Mu heavy-chain disease
- Gamma heavy-chain disease
- Alpha heavy-chain disease
- Monoclonal gammopathy of unknown significance (MGUS) IgG/A+
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition disease

Primary extranodal or nodal

- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue
- Nodal marginal zone B-cell lymphoma
  - Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - In situ follicular neoplasia
  - Duodenal-type follicular lymphoma
- Pediatric-type follicular lymphoma
- Large B-cell lymphoma with *IRF4 r*earrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL)-NOS
  - Germinal center B-cell type
  - Activated B-cell type
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system
- Primary cutaneous DLBCL, leg-type
- EBV+ DLBCL-NOS
- EBV+ muco-cutaneous ulcer

- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8+ DLBCL-NOS*
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration*
- Lymphomatoid granulomatosis
- High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* gene rearrangements*
- High-grade B-cell lymphoma NOS*
- B-cell lymphoma unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma

T and NK-cell Neoplasms

Predominantly disseminated

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Chronic lymphoproliferative disorder of NK cells*
- Systemic EBV-positive T-cell lymphoma of childhood*
- Chronic active EBV infection of T- and NK-cell type, systemic form
- Adult T-cell lymphoma/leukemia (HTLV-1+)

Primary extranodal

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the gastro-intestinal tract*
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Breast implant-associated anaplastic large cell lymphoma*
- Subcutaneous panniculitis-like T-cell lymphoma

Primary cutaneous

- Mycosis fungoides
- Sezary syndrome
- Primary cutaneous CD30 + lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Provisional CD4+ or CD8+ entities*
- Hydroa vacciniforme-like lymphoproliferative disorder
- Severe mosquito bite allergy

Predominantly nodal

- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with T follicular helper phenotype
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative

Hodgkin lymphomas

- **Nodular lymphocyte predominant Hodgkin lymphoma**
- **Classic Hodgkin lymphoma**
  Nodular sclerosis classic Hodgkin lymphoma
  Mixed cellularity classic Hodgkin lymphoma
  Lymphocyte-rich classic Hodgkin lymphoma
  Lymphocyte-depleted classic Hodgkin lymphoma

Immunodeficiency-associated lymphoproliferative disorders

Post-transplantation lymphoproliferative disorders (PTLD)
Non-destructive PTLD
  plasmacytic hyperplasia
  infectious mononucleosis PTLD
  florid follicular hyperplasia PTLD
Polymorphic PTLD
Monomorphic PTLD
Classic Hodgkin Lymphoma PTLD
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

* provisional entities

Figure legends

Figure 1

Evolution of lymphoma classifications (adapted from [99])

Figure 2

Histogenetic and pathogenetic model of mature B-cell neoplasms

The follicular (T-cell dependent) and extrafollicular pathways of normal B-cell differentiation are represented. Rearrangement of the IG heavy chain gene is symbolized with a horizontal bar in the nucleus, and somatic mutations in the IGV region are symbolized with vertical lines. The most common types of mature B-cell neoplasms are linked to their putative normal counterpart. The genetic lesion most frequently associated with each lymphoma category is also indicated.

Figure 3

Overview of the main peripheral T-cell lymphoma entities presenting as nodal diseases

The three groups of nodal lymphomas depicted on the scheme account for the majority of cases presenting with nodal involvement. The category of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is a diagnosis of exclusion, especially after having discarded the possibility of a TFH lymphoma (expressing at least two TFH markers), and after having excluded the possibility of nodal involvement by a disseminated T-cell neoplasm (T-cell prolymphocytic leukemia, adult T-cell leukemia/lymphoma) or an extranodal or cutaneous lymphoma. PTCL-NOS is a heterogenous category comprising several subsets defined by gene expression signatures resembling those of T Helper 1 or 2 cells (T-BET and GATA-3, respectively), EBV-positive tumors and neoplasms with a cytotoxic phenotype.

AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; F-TCL: follicular T-cell lymphoma; PTCL-TFH PTCL with follicular helper T-cell phenotype.

Figure 4

Evolution of the categorization of intestinal T-cell lymphomas

Primary intestinal T-cell lymphomas were collectively considered in the 2008 classification as one disease entity, enteropathy-associated T-cell lymphoma, of which two variants, type I (classical), and type II were recognized. In the 2017 classification, these two variants are considered as separate diseases, and designated enteropathy-associated T-cell lymphoma (EATL) (former type I) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (former type II). EATL is typically pleomorphic, often associated with an inflammatory component and necrosis. MEITL as its name implies, is composed of a monomophic lymphoid cell proliferation and infiltrates the adjacent epithelium of intestinal villi and crypts. In addition to EATL and MEITL, the current classification also recognizes a subset of cases not fulfilling the criteria for either EATL or MEITL, designated “intestinal T-cell lymphoma, not otherwise specified” as well as a category of indolent clonal T-cell

lymphoproliferative disorders. Moreover, other lymphoma types may present with intestinal involvement (for example extrandoal NK/T-cell lymphoma, ALK+ anaplastic T-cell lymphoma).

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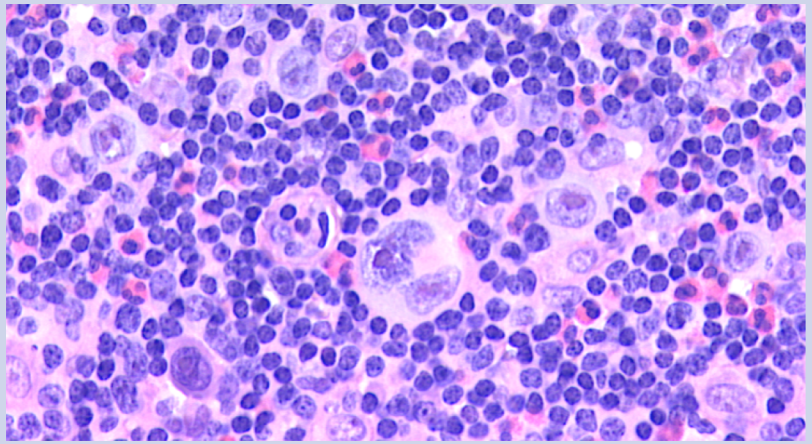
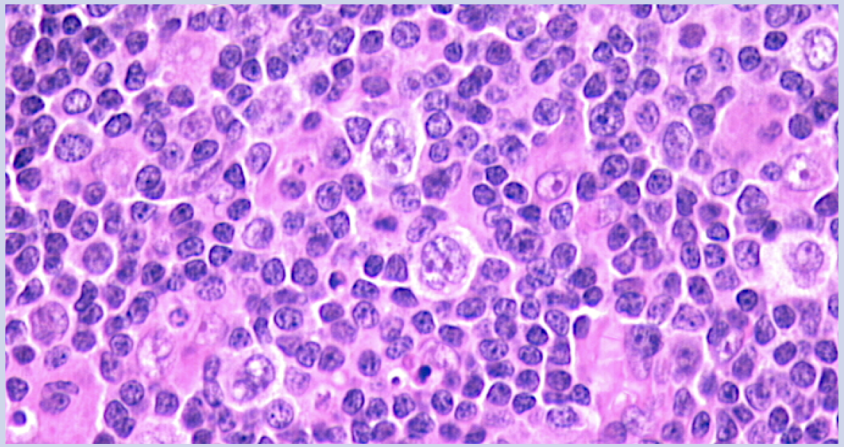
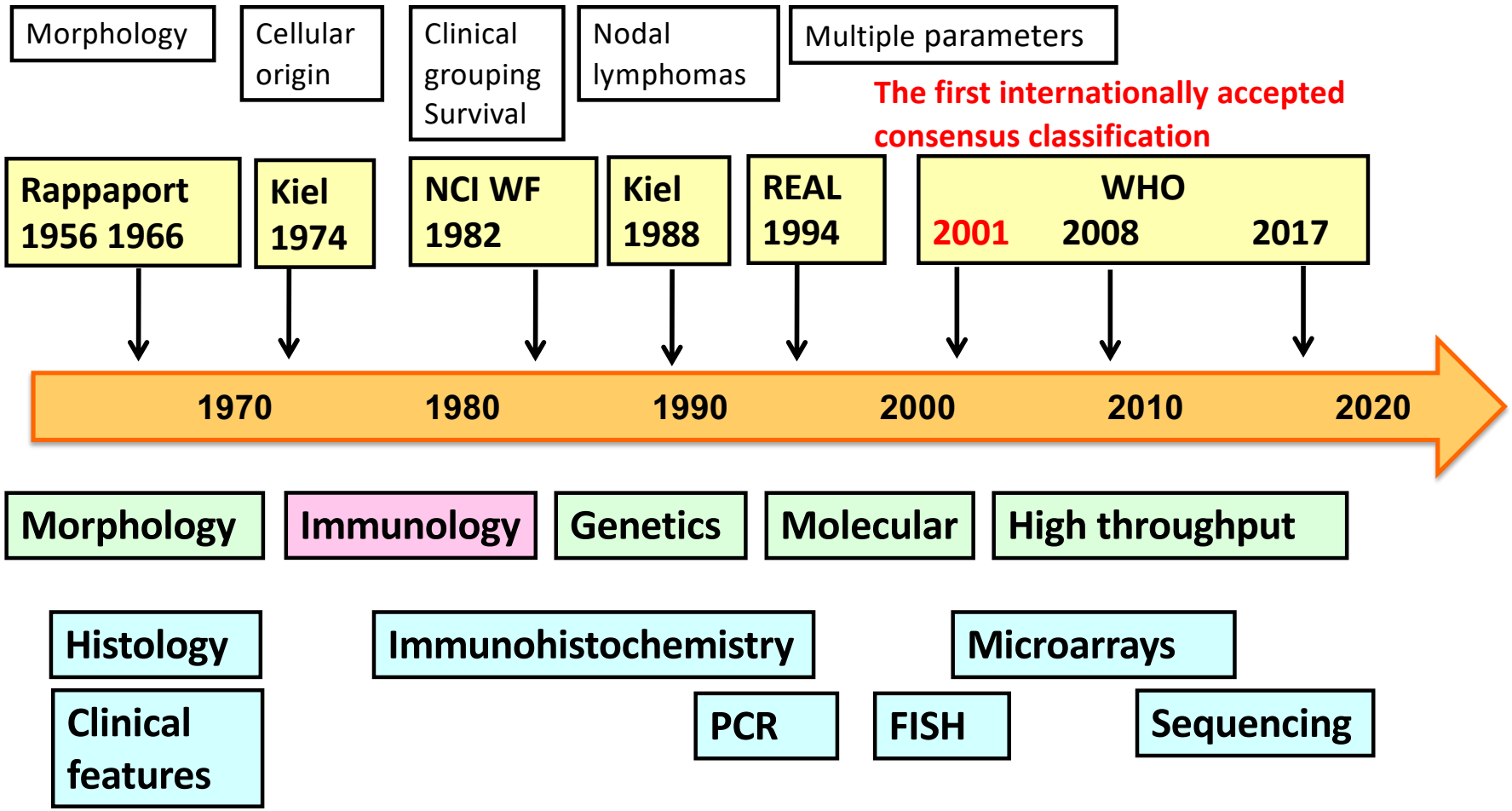
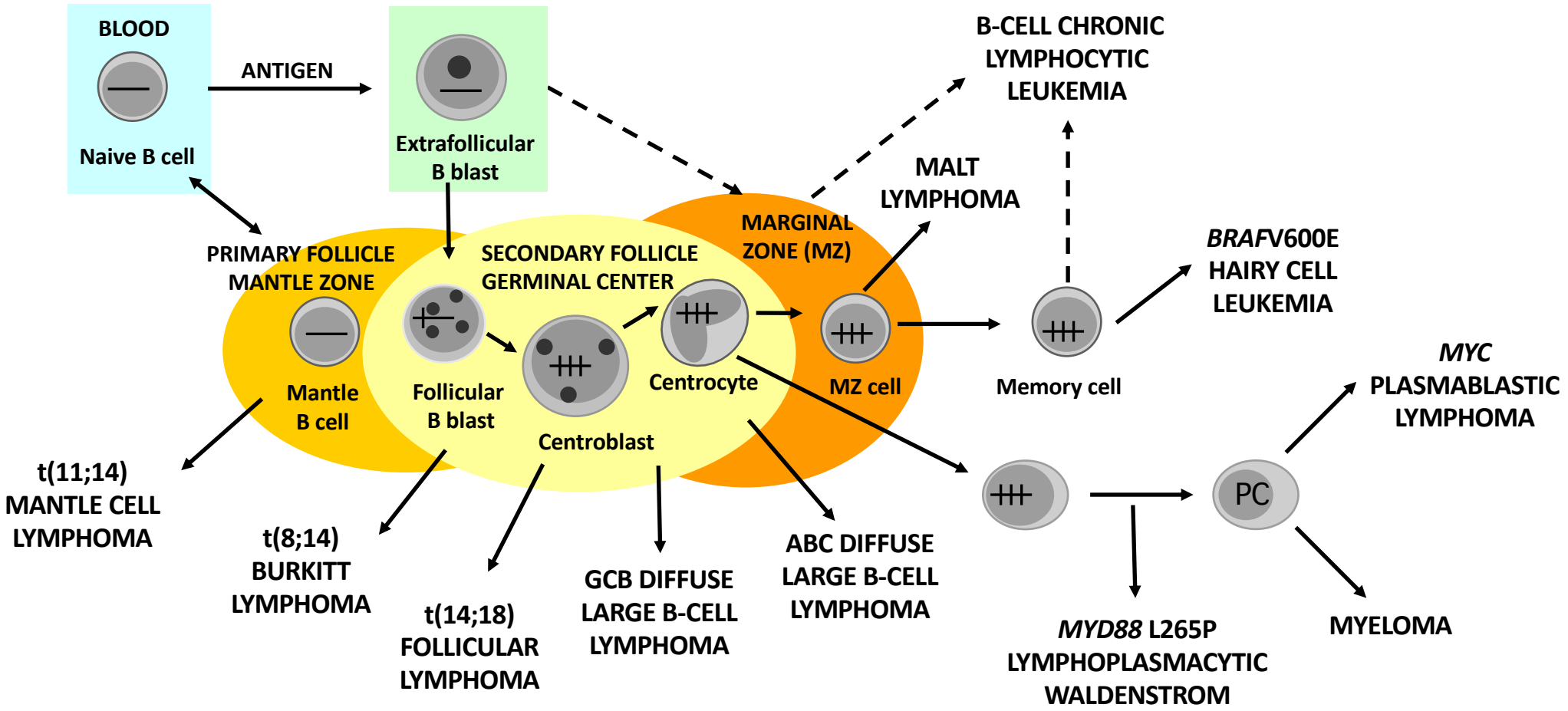
Table

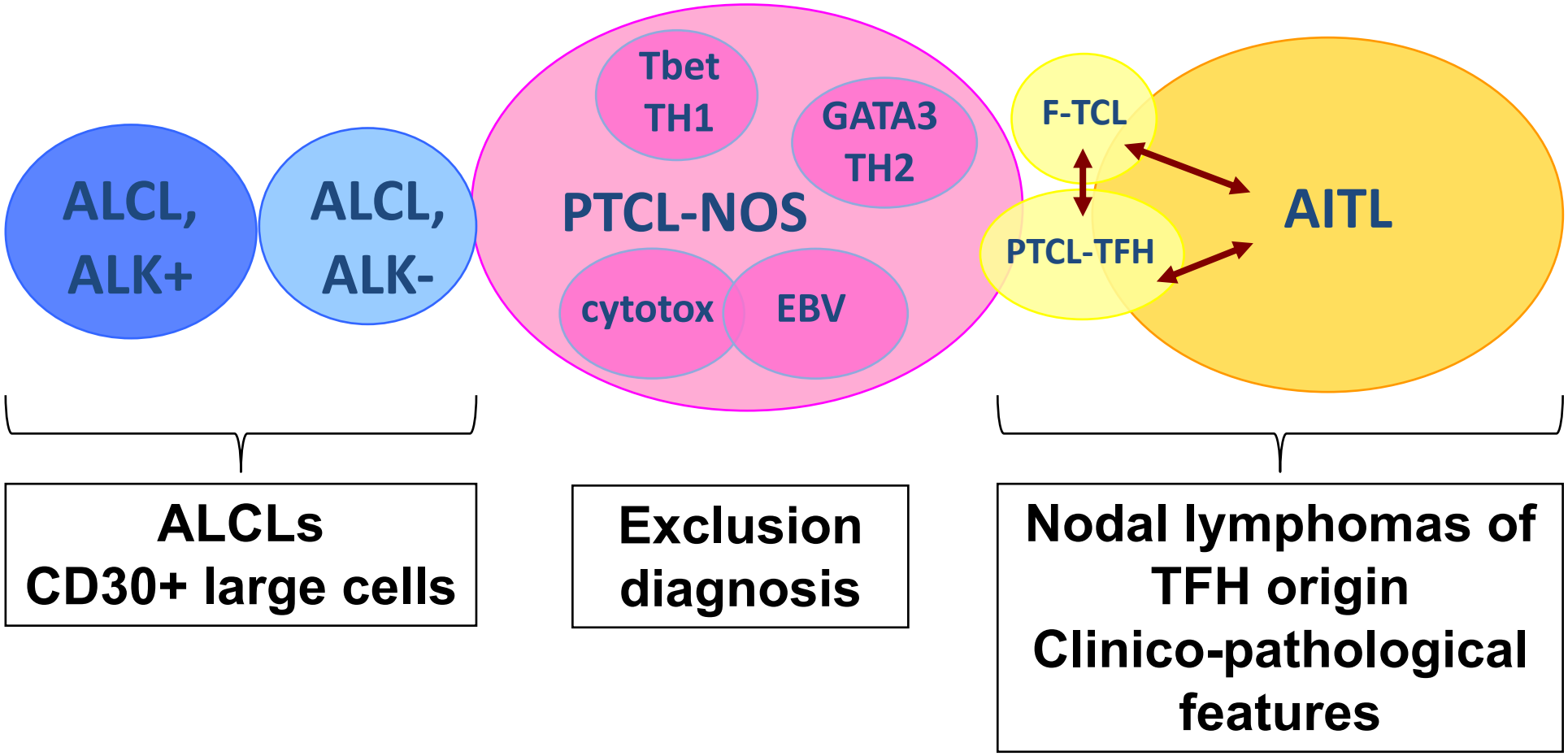
Table 2

Summary of distinguishing featrures of classic and nodular lymphocyte predomionant Hodgkin lymphomas

Classic Hodgkin Lymphoma (cHL) > 90% of HL	Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)
HRS cells: CD20-/+ PAX5+ CD30+ CD15+/- BCL6- MUM1+ BOB1- OCT2- EBV+ (40%) 	LP cells CD20+ PAX5+ CD30- CD15- BCL6+ MUM1+ BOB1+ OCT2+ EBV- 
Four types: Nodular Sclerosis and Mixed Cellularity most common; Lymphocyte-rich, or Lymphocyte–depleted less common	Six patterns: classical B-cell rich nodular (A), serpiginous/interconnexted (B); with promiennt extranodular LP cells (C); T-cell rich nodular (D); diffuse (T-cell/histiocyte-rich large B-cell lymphoma like) (E); diffuse B-cell-rich (F).
IG: clonal, mutated, crippled mutations Mutations in *STAT6, SOCS1*; *PDL1/PDL2* alterations, *CIITA* rearrangements	IG: clonal, mutated *BCL6* rearrangements, mutations in *DUSP2, JUN, SGK1, SOCS1*
Gray zone: unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and cHL	Gray zone: diffuse NLPHL versus T-cell/histiocyte-rich large B-cell lymphoma


Morphology
Cellular origin
Clinical grouping Survival
Nodal lymphomas
Multiple parameters
The first internationally accepted consensus classification
Rappaport 1956 1966
Kiel 1974
NCI WF 1982
Kiel 1988
REAL 1994
WHO
2001
2008
2017
1970
1980
1990
2000
2010
2020
Morphology
Immunology
Genetics
Molecular
High throughput
Histology
Clinical features
Immunohistochemistry
PCR
FISH
Microarrays
Sequencing


BLOOD
Naive B cell
ANTIGEN
Extrafollicular B blast
B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA
MALT LYMPHOMA
PRIMARY FOLLICLE MANTLE ZONE
SECONDARY FOLLICLE GERMINAL CENTER
MARGINAL ZONE (MZ)
BRAFV600E HAIRY CELL LEUKEMIA
Mantle B cell
Follicular B blast
Centroblast
Centrocyte
MZ cell
Memory cell
MYC PLASMABLASTIC LYMPHOMA
t(11;14) MANTLE CELL LYMPHOMA
t(8;14) BURKITT LYMPHOMA
t(14;18) FOLLICULAR LYMPHOMA
GCB DIFFUSE LARGE B-CELL LYMPHOMA
ABC DIFFUSE LARGE B-CELL LYMPHOMA
PC
MYD88 L265P LYMPHOPLASMACYTIC WALDENSTROM
MYELOMA


ALCL, ALK+
ALCL, ALK-
Tbet TH1
GATA3 TH2
PTCL-NOS
cytotox
EBV
F-TCL
PTCL-TFH
AITL
ALCLs CD30+ large cells
Exclusion diagnosis
Nodal lymphomas of TFH origin Clinico-pathological features

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA (classic, type I)

type II

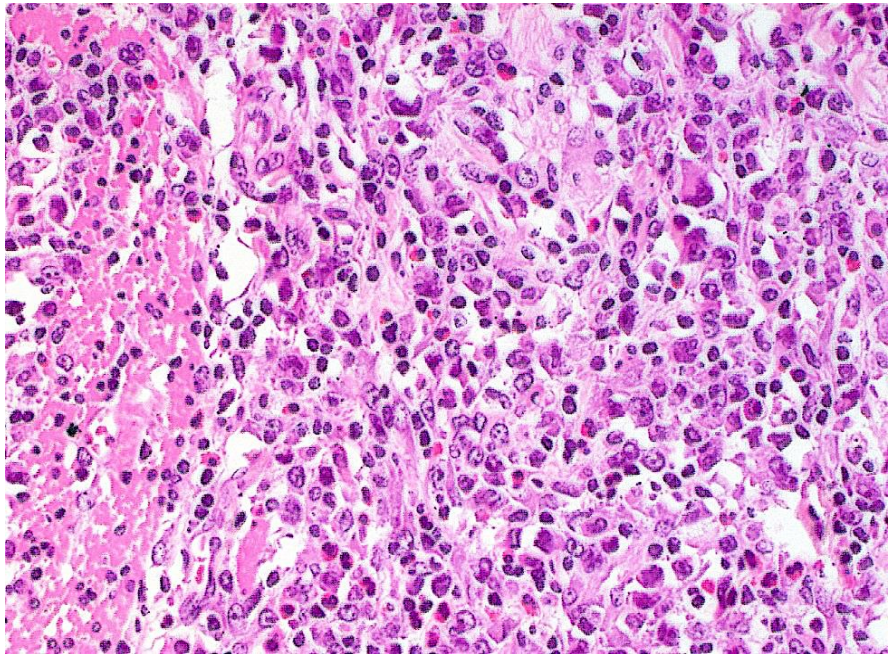
EATL

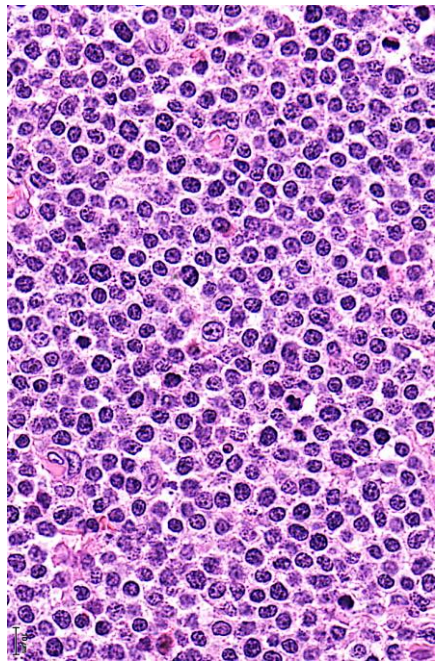
Other PTCLs

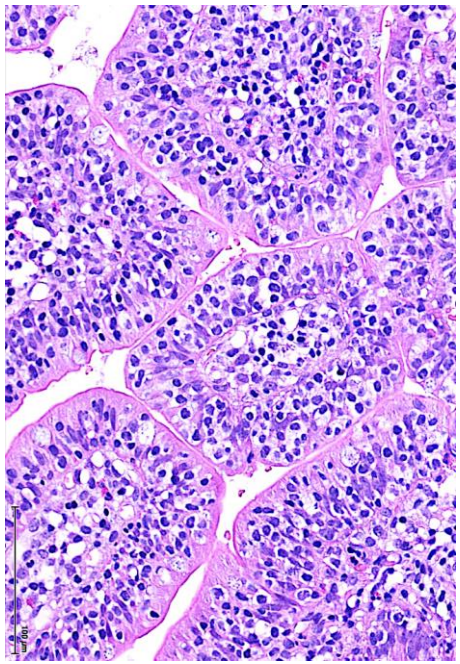
Intestinal TCL NOS

Indolent GI T-LPD

MEITL







WHO- 2008

WHO- 2017