

Diagnosis and classification of lymphoma: Impact of technical advances

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ABSTRACT

Our current understanding of the normal lymphoid system informs the modern classification of lymphomas. B-cell, T-cell, and natural killer-cell neoplasms often recapitulate normal stages of lymphoid cell differentiation and function. Moreover, the clinical manifestations of lymphomas often reflect the normal function of lymphoid cells *in vivo*. The multiparameter approach to classification adopted by the Revised European and American Lymphoma and subsequent WHO classifications facilitates the interpretation of clinical and translational studies, and provides a framework for the discovery of molecular alterations that drive these tumors. An accurate and precise classification of disease entities facilitates the discovery of the molecular basis of lymphoid neoplasms in the basic science laboratory, and leads to new diagnostic tools that play a role in clinical diagnosis.

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Introduction

Mature B-cell and T- and/or natural killer (NK)-cell neoplasms are clonal tumors of B-cells, T-cells, or NK-cells that in many respects recapitulate stages of normal B-cell or T-cell differentiation. The ability to identify the cell lineage of lymphoid cells has shaped the modern classification of lymphomas, and is a starting point for diagnosis. It has been tempting to base the classification of lymphoid malignancies strictly on the corresponding normal stage of differentiation. However, for some neoplasms, such as hairy cell leukemia, a normal cellular counterpart has not been distinguished. Similarly, some neoplasms are not strictly defined based on the cellular origin; for example, hepatosplenic T-cell lymphomas derived from alpha-beta or gamma-delta T-cells show similar genetic aberrations and clinical features.

Cancer is increasingly recognized as a genetic disease, with precise molecular alterations often defining entities. However, it is apparent that similar genetic aberrations can be associated with divergent disease entities. Translocations of *ALK* are the hallmark of anaplastic large cell lymphoma [1], an aggressive T-cell lymphoma common in childhood, but the *ALK* translocation is a characteristic of an aggressive form of B-cell lymphoma, *ALK*-positive large B-cell lymphoma, a tumor exhibiting plasmablastic differentiation [2,3]. Moreover, the role of *ALK* is not restricted to lymphomas, and is also associated with a rare form of histiocytosis seen in infancy [4].

The basic principle of the Revised European and American Lymphoma (REAL) classification was to define disease entities based on a constellation of features including morphology, clinical fea-

tures, immunophenotype, and genetic features [5]. The proponents, members of the International Lymphoma Study Group, recognized that no one feature was sufficient, and that multiple parameters must be considered. The principles of the REAL classification were adopted by the architects of the WHO classification, and extended to the classification of all hematolymphoid neoplasms, inclusive of myeloid and histiocytic tumors [6]. As the field has matured and progressed, these guiding principles for disease definition have served us well, and have allowed for the incorporation of new data from evolving technical advances, as outlined in elsewhere in this volume. Not surprisingly, the classification of lymphoma has continued to evolve from the REAL classification published in 1994 [5], to the WHO classification first published in 2001 [6], and updated in successive revisions in 2008 [7] and most recently in 2017 [8,9]. The latest revision is a collective effort of 12 editors and senior advisors, and contributions from more than 200 pathologists, geneticists, and clinicians (Table 1). This review will touch on several aspects of the latest iteration of the WHO classification of lymphomas, in which technical insights have informed our understanding of disease entities, and led to revisions in the classification.

Early lesions—Lymphoid neoplasms of low malignant potential

Our knowledge of disease-specific genetic and phenotypic alterations has resulted in the detection of clonal lymphoid lesions sharing genetic and/or phenotypic aberrations with well-defined neoplasms such as chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL and SLL), multiple myeloma, follicular lymphoma (FL), duodenal-type follicular lymphoma (DTFL), and mantle cell lymphoma (MCL) without fulfilling diagnostic criteria for overt malignancy [10]. Besides DTFL, these are specifically designated in the WHO classification as monoclonal B-lymphocytosis (MBL), *in-situ* follicular neoplasia (ISFN), and *in-situ* mantle cell neoplasia [8].

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Table 1.
WHO classification of mature lymphoid neoplasms: Revised 4th Edition.#

Mature B-cell neoplasms

Chronic lymphocytic leukaemia and/or small lymphocytic lymphoma
 Monoclonal B-cell lymphocytosis
 B-cell prolymphocytic leukaemia
 Splenic marginal zone lymphoma
 Hairy cell leukaemia
Splenic B-cell lymphoma and/or leukaemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukaemia-variant
 Lymphoplasmacytic lymphoma
 Monoclonal gammopathy of undetermined significance (MGUS), IgM
 Gamma heavy chain disease
 Mu heavy chain disease
 Alpha heavy chain disease
 Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
 Plasma cell myeloma
 Solitary plasmacytoma of bone
 Extracranial plasmacytoma
 Monoclonal immunoglobulin deposition diseases
 Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
 Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
 Follicular lymphoma
 In situ follicular neoplasia
 Pediatric type follicular lymphoma
Large B-cell lymphoma with IRF4 rearrangement
 Primary cutaneous follicle center lymphoma
 Mantle cell lymphoma
 In situ mantle cell neoplasia
 Diffuse large B-cell lymphoma, NOS
 Germinal center type
 Activated B-cell and/or nongerminal center type
 T-cell and/or histiocyte-rich large B-cell lymphoma
 Primary DLBCL of the CNS
 Primary cutaneous DLBCL, leg type
 EBV positive DLBCL, NOS
 EBV+ mucocutaneous ulcer
 DLBCL associated with chronic inflammation
 Lymphomatoid granulomatosis
 Primary mediastinal (thymic) large B-cell lymphoma
 Intravascular large B-cell lymphoma
 ALK positive large B-cell lymphoma
 Plasmablastic lymphoma
 Primary effusion lymphoma
 HHV8-positive DLBCL, NOS
 Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
 High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
 High grade B-cell lymphoma, NOS
 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T-and NK-neoplasms

T-cell prolymphocytic leukaemia
 T-cell large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK cells
 Aggressive NK cell leukaemia
 Systemic EBV+ T-cell Lymphoma of childhood
 Hydroa vacciniforme-like lymphoproliferative disorder
 Adult T-cell leukaemia and/or lymphoma
 Extranodal NK- and/or T-cell lymphoma, nasal type
 Enteropathy-associated T-cell lymphoma
 Monomorphic epitheliotropic intestinal T-cell lymphoma
Indolent T-cell lymphoproliferative disorder of the GI tract
 Hepatosplenic T-cell lymphoma
 Subcutaneous panniculitis-like T-cell lymphoma
 Mycosis fungoides
 Sézary syndrome
 Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
 Lymphomatoid papulosis
 Primary cutaneous anaplastic large cell lymphoma
 Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder
 Peripheral T-cell lymphoma, NOS

(continued on next page)

Table 1. (continued)

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|---|
| Angioimmunoblastic T-cell lymphoma |
| <i>Follicular T-cell lymphoma</i> |
| <i>Nodal peripheral T-cell lymphoma with TFH-like phenotype</i> |
| Anaplastic large cell lymphoma, ALK positive |
| Anaplastic large cell lymphoma, ALK negative |
| <i>Breast implant-associated anaplastic large cell lymphoma</i> |
| Hodgkin lymphoma |
| Nodular lymphocyte predominant Hodgkin lymphoma |
| Classical Hodgkin lymphoma |
| Nodular sclerosis classical Hodgkin lymphoma |
| Lymphocyte-rich classical Hodgkin lymphoma |
| Mixed cellularity classical Hodgkin lymphoma |
| Lymphocyte-depleted classical Hodgkin lymphoma |

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; GI = Gastrointestinal; NK = natural killer; NOS = not otherwise specified; TFH = T follicular helper.

* Post-transplant lymphoproliferative disorders are not listed. Provisional entities are listed in *italics*.

The widespread use of flow cytometric analysis led to the detection of low levels of clonal B-cell populations with CLL-like immunophenotype in asymptomatic individuals with normal peripheral blood counts, termed MBL [11]. MBL is defined as the presence of a circulating monoclonal B-cell population below $5 \times 10^9/L$, ($5000/\mu L$), persisting for at least 3 months, in otherwise asymptomatic individuals [12]. MBL is now subdivided into high-count MBL (0.5 – $5.0 \times 10^9/L$) and low-count MBL ($<0.1 \times 10^9/L$) [13]. High-count MBL has the highest prevalence amongst first-degree relatives of patients with CLL [14] and unlike low-count MBL, has *IGHV* mutations with a repertoire similar to CLL suggesting a biological relationship [15–17]. However, both high-count and low-count MBL show CLL-related cytogenetic alterations including *del(13q)*, *+12* and *del(17p)*, albeit at lower levels, suggesting that these changes occur early in clonal evolution and are not prognostically significant in the absence of B-cell lymphocytosis [18]. We know that virtually all cases of clinical CLL are preceded by a phase of MBL. High-count MBL progresses to CLL at an annual rate of 1% to 2% with the clonal B-cell count at presentation being the biggest risk factor. This contrasts with low-count MBL, which presents without evident lymphocytosis and does not require clinical monitoring for progression. Additionally, there are cases of MBL with a non-CLL phenotype with a suggested relationship to marginal zone lymphoma (MZL) [17].

Follicular lymphoma *in situ* was initially described as the localization of atypical B-cells with strong expression of CD10 and BCL-2 in the germinal centers of reactive-appearing lymph nodes [19]. These cells have the *t(14;18)(IGH-BCL2)* translocation, seen in approximately 85% of overt low grade FL, but carry a very low level of other genetic aberrations, in comparison with clinically evident FL. The risk of progression to FL is now known to be very low, less than 5%, if there is no clinical evidence of FL at the time of diagnosis [20,21]. The WHO classification proposed the term ISFN, rather than *in situ* FL, to avoid unnecessary patient anxiety and potential overtreatment of patients with this lesion. In fact, the *t(14;18)* can be detected using sensitive methods in up to 70% of healthy adults over the age of 50, indicating that the translocation itself is a common finding of low clinical risk, although a high mutational load in the blood may be an indication of evolving FL [22].

DTFL shares many features with ISFN, including a low risk of progression, and a low level of genetic aberrations. Most cases are diagnosed on endoscopy, often performed for reasons unrelated to the subsequent DTFL diagnosis. Endoscopic features include solitary or multiple polyps, mucosal nodularity or plaques, most common in the duodenum but also seen in other sites of the small bowel [23]. The risk of progression and dissemination is generally less than 5%. The atypical CD10+, BCL-2+ B-cells infiltrate the lamina propria, and distort the villi. Molecular testing for *IGH* clonality or cytogenetics and/or fluorescence *in situ* hybridization (FISH)

analysis for *t(14;18)(IGH-BCL2)* is positive in the majority of cases [23].

A second group of “indolent” or indeterminate clonal lymphoid proliferations do not have a counterpart among the currently recognized subtypes of lymphoma, but appear to have a limited potential for progression. Their optimal therapeutic management has been ambiguous and recent data suggest that conservative management may be sufficient in most cases. Included in this group pediatric-type FL, and a number of T-cell proliferations of low malignant potential: primary cutaneous CD4-positive T-cell lymphoproliferative disease (LPD), primary cutaneous acral CD8-positive T-cell lymphoma, indolent T-cell LPD of the gastrointestinal tract, and breast-implant associated T-cell lymphoma.

The pediatric-type of FL differs from the adult counterpart morphologically, immunophenotypically, and genetically [24,25]. It presents predominantly in young males, most often as isolated cervical lymphadenopathy. Most patients achieve long term disease free survival following excision of an isolated mass lesion, and additional chemotherapy is generally not advised. The tumor lacks the characteristic *t(14;18)(IGH-BCL2)* translocation, and is most often negative for BCL-2 protein as well. While lacking the genetic hallmarks of FL, recent studies have identified other recurrent genetic aberrations. A high proportion of cases have mutations in *TNFRSF14* [26], often with copy-number neutral loss at 1p36. In addition, a high proportion of cases have mutations affecting genes in the MAPK pathway, most commonly *MAP2K* [27,28].

Several indolent clonal T-cell proliferations are recognized in the revised WHO classification. Primary cutaneous CD4-positive T-cell LPD was provisional in the 2008 classification, but was renamed as a “LPD”, rather than lymphoma. It usually presents as an isolated cutaneous lesion, often on the face or head, and contains a mixed of both B- and T-lymphocytes. The T-cells express some T follicular helper markers, and are clonal, but most cases respond to local therapy of the single lesion, and recurrent genetic aberrations have not been recognized [29]. Primary cutaneous acral CD8-positive T-cell lymphoma [30], indolent T-cell LPD of the gastrointestinal tract [31], and breast-implant associated T-cell lymphoma [32] are all listed as provisional entities.

Small B-cell neoplasms

Refinements have occurred in the understanding of small B-cell lymphomas. A long-standing problem had been the differential diagnosis of lymphoplasmacytic lymphoma (LPL) and MZL, since both are usually associated with plasmacytic differentiation in the neoplastic cells. The identification of the *MYD88* L265P mutation in most cases of LPL but only rarely in MZL has provided new tools for diagnosis [33]. The association of *MYD88* L265P and mutations in *CXCR4* has segregated IgM monoclonal gammopathy of undetermined significance from other forms of monoclonal gammopathy

of undetermined significance, placing it as closely related to LPL and Waldenström's macroglobulinemia [34–36].

MCL has been recognized as showing greater heterogeneity in clinical behavior and phenotype than previously appreciated. *Leukemic non-nodal MCL* has been delineated as a distinct variant associated with frequent splenomegaly, bone marrow and peripheral blood involvement, infrequent peripheral lymphadenopathy, and an indolent clinical course [37,38]. This variant is negative for SOX11, in contrast to classical MCL, and is usually derived from IGHV mutated B-cells. These cases had often been mistaken for CLL previously. SOX11 immunohistochemistry has also proved to be useful in recognizing rare cases of classical MCL that are negative for cyclin D1 [39].

The basic approach to grading FL remains unchanged. However, there is improved understanding of some FL variants, such as FL negative for CD10 (often positive for IRF4 and/or MUM1) and cases of FL negative for t(14;18) [40]. Studies have provided new insights in the genetic heterogeneity of FL, with the possibility that analysis of the mutational profile will be incorporated in the future for assessment of clinical risk and protocol assignment [41]. Additionally, there is more formal recognition that FL, Grade 3B, is biologically and clinically related to diffuse large B-cell lymphoma (DLBCL) [42].

Aggressive B-cell neoplasms

A significant change in the classification of diffuse large B-cell lymphomas is the recommendation that routine practice should recognize tumors belonging to the germinal center B-cell (GCB) and activated B-cell (ABC) subsets using either immunohistochemical surrogates or other means, as they may become available [8,43,44]. This subdivision has proven prognostic value, and also correlates with significant differences in the molecular pathogenesis of the tumors. Recent studies also have shown that ABC vs GCB lymphomas exhibit differential sensitivity to certain drugs, which may direct patient management in the near future [45]. Finally, it has become clear that most double-hit lymphomas fall within the GCB subgroup; thus, determination of cell of origin can facilitate identification of those tumors that should undergo FISH for *MYC* rearrangement [46]. While routine gene expression profiling is currently beyond the reach of most clinical laboratories, new techniques are making these determinations possible, even with formalin-fixed paraffin embedded tissue specimens [43,44].

The 2008 WHO classification included a borderline category, termed B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (often referred to informally as “high grade unclassifiable” or HGLUC). This group, admittedly heterogeneous, was used to designate high grade B-cell neoplasms that had intermediate cytologic features between DLBCL and BL. Many cases diagnosed as HGLUC were so-called double-hit or more rarely triple-hit lymphoma, carrying translocations involving *MYC*, and either or both *BCL2* and *BCL6* [47,48]. Moreover, clinical studies indicated that most of these double-hit lymphomas were clinically aggressive with a poor outcome when treated with conventional chemotherapy, such as R-CHOP. However, it also became apparent that double-hit lymphomas were morphologically heterogeneous, such that some were diagnosed as DLBCL, while others, based on intermediate cytology, were classified as HGLUC [49]. The division of what appeared to be a genetically homogeneous group of tumors into 2 different diagnostic categories led to difficulties in evaluating this subgroup in clinical trials and evaluating current and evolving therapeutic regimens. Thus, the clinical advisory committee agreed on the creation of a unifying category designated as *High grade B-cell lymphoma, with rearrangements of MYC and BCL2 and/or BCL6*. Notably,

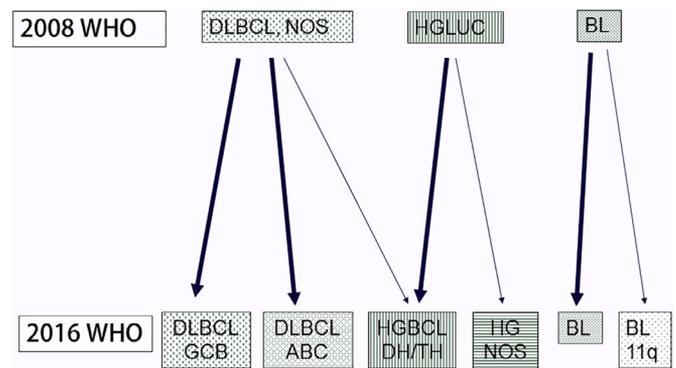


Fig. 1. Navigating changes in the classification of aggressive B-cell lymphomas. The categories of diffuse large B-cell lymphoma (DLBCL), NOS, High-grade B-cell lymphoma unclassified, and Burkitt lymphoma have undergone refinement and redefinition as shown. DLBCL should be designated as GCB or ABC for clinical purposes. High grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBCL DH/TH) is now segregated as a separate entity, which can have a varied morphologic appearance, in some cases resembling DLBCL, NOS. Rare lymphomas closely resembling Burkitt lymphoma may lack a *MYC* rearrangement, but instead have aberrations at 11q. ABC=activated B-cell; GCB=germinal center B-cell; NOS=not otherwise specified.

this category excludes cases of B-lymphoblastic lymphoma and/or leukemia, which may be “double hit” as a consequence of progression from FL [50–52].

Importantly, the WHO classification distinguishes between double-hit lymphomas, and tumors that have increased protein expression for *BCL2* and *MYC* in the absence of dual translocations, often termed “double expressor” (DE) tumors. DE lymphomas are enriched in DLBCL of the ABC subtype of DLBCL [46,53,54]. Dual expression of *MYC* and *BCL2* is an adverse prognostic factor, but this may be based, at least in part, on factors related to the ABC designation (Fig. 1).

There remains a small group of tumors that are perceived to be cytologically “high grade”, perhaps requiring more aggressive therapy. These are designated as “high grade, not otherwise specified”, and by definition exclude double-hit lymphomas, and BL. This designation should be used sparingly, and is not simply based on a high proliferation fraction with Ki-67 [8]. However, such cases may show overlapping features with BL.

The definition of BL is essentially unchanged in the revised classification. However, there is a rare variant of high grade B-cell lymphoma that closely resembles BL but lacks the *MYC* translocation, and instead has frequent aberrations involving the 11q region. These cases occur mainly in children, and are more often nodal than extranodal, in contrast to BL [55]. They are clinically aggressive, but have a good response to therapy. It is notable that the same 11q aberration is found in some cases of BL with the *MYC* translocation, so it is not specific to this new provisional entity [56].

Large B-cell lymphoma with IRF4 rearrangement is a newly recognized provisional entity, which occurs almost exclusively in children and young adults [57,58]. These lymphomas most typically occur in Waldeyer ring or head and neck lymph nodes and are low stage. Most cases have at least a partial follicular growth pattern resembling FL grade 3B, but diffuse areas consistent with DLBCL are common. They show strong expression of IRF4/MUM1, as well as being positive for *BCL6* and CD10. They are most often of germinal center type, particularly based on gene expression profiling studies [57]. Most cases have *IRF4* rearrangements sometimes together with *BCL6* rearrangements but they uniformly lack *BCL2* rearrangements. However, rearrangements of *IRF4* are inconsistent demonstrated by FISH studies.

Epstein-Barr virus (EBV)-positive DLBCL of the elderly was a provisional entity in the 2008 WHO classification [7]. Since then greater insight has been achieved regarding the epidemiology and prognostic significance of EBV in DLBCL. For one, the age distribution of EBV-positive DLBCL is much broader than originally thought, and is not restricted based on age [59,60]. Interestingly, while EBV is an adverse prognostic factor in older patients [61,62], younger patients appear to have a better prognosis [59]. EBV-positive large B-cell lymphomas in young patients are more often nodal, while the preponderance of cases in the elderly has an extranodal component.

The WHO classification also recognizes EBV-positive mucocutaneous ulcer (EBV-MCU), as a localized lesion with a good prognosis and low risk of progression or dissemination [63,64]. EBV-MCU presents in patients with decreased immune surveillance for EBV, either related to advanced age, iatrogenic immune suppression, or other factors such as HIV infection. The most common site of presentation is the oral cavity, including gingiva, but skin and intestinal mucosa also can be involved. Distinction from EBV-positive DLBCL and classical Hodgkin's lymphoma, both of which share some morphologic features, is important because of very different treatment implications. Most patients with EBV-MCU can be managed conservatively [65].

Peripheral T-cell lymphomas

There has been progress in illuminating the genetic landscape and classification of mature T-cell lymphomas. Genetic studies have shown recurrent mutations that affect a significant proportion of cases of angioimmunoblastic T-cell lymphoma. Importantly, many of same genetic changes are observed in cases of peripheral T-cell lymphomas (PTCL), NOS that manifest a TFH phenotype [66–68]. For this designation, the neoplastic cells should express at least 2 or 3 TFH-related antigens among PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5. These observations have led to *follicular T-cell lymphoma*, *angioimmunoblastic T-cell lymphoma*, and *nodal PTCL with a TFH phenotype* being unified under a common heading.

Genomic approaches also have provided insights into the spectrum of CD30-expressing T-cell lymphomas, and have facilitated the distinction of PTCL with high CD30 expression and ALK-negative anaplastic large cell lymphoma (ALCL), the latter having a superior prognosis [69]. Studies have further elucidated the genetic complexity of ALK-negative ALCL, which is no longer a provisional category. Additionally, this genetic complexity provides important prognostic information; for example, cases of ALK-negative ALCL with *DUSP22* translocation have an excellent prognosis, while cases with *TP63* rearrangements have a very poor outcome [70]. Newly incorporated into the revised WHO classification is *Breast-implant associated ALCL*, which morphologically and phenotypically resembles other forms of ALCL, but has very different clinical behavior. If neoplastic cells are confined to the seroma fluid surrounding the implant, patients can be managed conservatively with implant removal but no further therapy [32].

Recent data also have led to changes in the categorization of intestinal T-cell lymphomas. It has become apparent that the 2 subtypes of enteropathy associated T-cell lymphoma (EATL) are distinct, now clearly distinguished in the revised WHO classification. EATL, Type I, now simply designated as *Enteropathy-associated T-cell lymphoma*, is closely linked to celiac disease, and is primarily a disease of individuals of northern European origin. EATL, type II, now formally designated as *Monomorphic epitheliotropic intestinal T-cell lymphoma*, shows no association with celiac disease, and appears increased in incidence in Asians, and Hispanic populations [71,72]. There remains a small group of intestinal T-cell lymphomas that do not meet criteria for EATL or Monomorphic epitheliotropic intestinal T-cell lymphoma as currently defined. These should be

designated as intestinal T-cell lymphoma, not otherwise specified. All of the above should be distinguished from indolent T-cell LPD of the gastrointestinal tract [31].

EBV-positive T-cell and NK-cell neoplasms

Extranodal NK/T-cell lymphoma, nasal type has been recognized for many years, and its definition is largely unchanged. It most commonly presents in the upper aero digestive tract, and is most often of NK-cell origin, but T-cell cases exist. However, the designation of other EBV-positive T-cell neoplasms has undergone some modification in the 2017 WHO classification [8]. EBV-associated T- and NK-cell lymphoproliferative disorders, most often presenting in the pediatric age group, include 2 major groups: chronic active EBV-infection, and systemic EBV-positive T-cell lymphoma of childhood [73,74]. Both occur with increased frequency in Asians, and in Native American populations from Central and South America and Mexico. chronic active EBV-infection of T/NK type shows a broad range of clinical manifestations from indolent, localized forms such as hydroa vacciniforme-like lymphoproliferative disorder and severe mosquito bite allergy to a more systemic form characterized by fever, hepatosplenomegaly and lymphadenopathy, with or without cutaneous manifestations [75,76]. Systemic EBV+ T-cell lymphoma of childhood—no longer referred to as a “lymphoproliferative disorder”—has a very fulminant clinical course usually associated with a hemophagocytic syndrome. The differential diagnosis includes acute EBV-associated hemophagocytic lymphohistiocytosis, which can present acutely, but in some patients responds well to the hemophagocytic lymphohistiocytosis 94 protocol, and is not considered neoplastic [77]. Node-based EBV-positive PTCL are uncommon and included under the broad heading of PTCL, NOS. They are generally monomorphic and lack the angioinvasion and necrosis of extranodal NK/T-cell lymphoma. They most often present in older adults, and rarely in the post-transplant setting and other immunodeficiency states [71,78,79].

Conflict of interest

No financial disclosures and no potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1053/j.seminhematol.2018.05.007](https://doi.org/10.1053/j.seminhematol.2018.05.007).

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