Peer reviewed article

Who is *WHO* and what was *REAL*?

A review of the new WHO classification (2001) for malignant lymphomas

Sergio B. Cogliatti, Ulrico Schmid

Department of Pathology, Cantonal Hospital St. Gallen, Switzerland

Summary

The principles of the new WHO classification of haematopoietic and lymphoid tumours are based on those defined in the *R*evised *E*uropean *A*merican classification of *L*ymphoid neoplasms (REAL), published by the *I*nternational *L*ymphoma *S*tudy *G*roup (ILSG) in 1994. Thus, the new WHO classification may be considered an updated version of the REAL classification rather than of the old WHO classification published in 1976. Disease entities are defined on the basis of *morphological*, *phenotypic*, *genotypic*, and *clinical* data. The relative impact of these characteristics varies among different diseases and there is "*no gold standard*". Thus, the strict hierarchy among diagnostic criteria, headed by morphology and followed by immunohistochemistry and genetics, has been discontinued. The WHO classification not only encompasses lymphoid tumours but extends to myeloid, mast cell and histiocytic/dendritic cell malignancies. Neoplasms are primarily stratified according to their tumour cell lineage. For each neoplasm a cell of origin is postulated. The classification of lymphoid malignancies recognises three major categories, B-cell neoplasms, T-/NK-cell neoplasms, and Hodgkin lymphomas. B-cell and T-cell lymphomas are further divided into precursor neoplasms and mature neoplasms, the latter being subdivided according to their clinical manifestation into disseminated/leukaemic, extranodal and nodal malignancies. In contrast to previous classifications, the neoplasms are grouped neither according to their histological grade (Kiel classification) nor according to their clinical aggressiveness (International Working Formulation). However, the histological grade is considered a prognostic factor which enters into the description of each disease entity. Hodgkin's disease, now more appropriately termed Hodgkin lymphoma, comprises nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphomas of nodular sclerosis, mixed cellularity, lymphocyte-depleted and lymphocyte-rich subtype.

For practical purposes this minireview disregards the description of myeloid, macrophage/histiocytic, dendritic cell and mast cell disorders. Furthermore, the present paper is restricted to those lymphoid tumours that are not already identically described in the REAL classification, in order to focus on what is *really* new in the WHO classification.

Key words: lymphoma classification; WHO; REAL; Kiel; non-Hodgkin lymphoma; Hodgkin lymphoma

Alphabetic list of abbreviations

ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
bcl-2 / bcl-6	B-cell lymphoma/leukaemia –2/–6 oncogenes
Bob-1	transcriptional factor
BSAP	B-cell specific activator protein
CD	cluster designation
CLL	chronic lymphocytic leukaemia
c-myc	human proto-oncogene
DLBCL	diffuse large B-cell lymphoma
LMP-EBV	latent membrane protein of the Epstein-Barr virus
EMA	epithelial membrane antigen
FL	follicular lymphoma
HHV8	human herpes virus 8
HIV	human immunodeficiency virus
HTLV-1	human T-cell lymphotropic virus
Ig-V_H	immunoglobulin heavy chain variable genes
IWF	International Working Formulation
ILSG	International Lymphoma Study Group
Ki-1	monoclonal mouse anti-human CD30 (clone Ber-H_2)
KSHV	Kaposi sarcoma herpes virus
LDH	lactate dehydrogenase
LPL	lymphoplasmacytic lymphoma
MALT	mucosa-associated lymphoid tissue
NPM	nucleophosmin
Oct-2	transcriptional factor
PLL	prolymphocytic leukaemia
PTLD	post transplant lymphoproliferative disorder
REAL	Revised European American Classification of Lymphoid Neoplasms
SLL	small lymphocytic lymphoma
SMZL	splenic marginal zone lymphoma
TdT	terminal deoxynucleotidyl transferase
WHO	World Health Organisation

The authors thank the SAKK (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung) for its financial support.

Table 1

Entities of the WHO classification for lymphoid neoplasms (2001) and their equivalents in the updated Kiel classification (1992) and the REAL classification (1994). *Provisional entities* of the REAL classification are printed in *italics.* Major differences between the WHO and the REAL classification, as described in the text, are underlaid with colour. By accident, diffuse large B-cell lymphoma and intravascular large B-cell lymphoma are given the same code-number (9680/3) in the original literature [8]. This mistake has been reported to one of the editors of the WHO book.

Kiel (updated) 1992	REAL 1994	WHO 2001	ICD-O code
B-cell lymphomas	**B-cell neoplasms**	**B-cell neoplasms**	
	Precursor B-cell neoplasm	**Precursor B-cell neoplasm**	
Acute lymphoblastic B-cell leukaemia B lymphoblastic lymphoma	Precursor B lymphoblastic leukaemia / lymphoma	Precursor B lymphoblastic leukaemia / lymphoma	9835 / 3 9728 / 3
	Peripheral B-cell neoplasms	**Mature B-cell neoplasms**	
B-cell chronic lymphocytic leukaemia	B-cell chronic lymphocytic leukaemia /	Chronic lymphocytic leukaemia /	9823 / 3
Immunocytoma, lymphoplasmacytoid type	small lymphocytic lymphoma /	small lymphocytic lymphoma	9670 / 3
B-cell prolymphocytic leukaemia	B-cell prolymphocytic leukaemia	B-cell prolymphocytic leukaemia	9833 / 3
Immunocytoma, lymphoplasmacytic type	Lymphoplasmacytoid lymphoma / immunocytoma	Lymphoplasmacytic lymphoma	9671 / 3
	Splenic marginal zone lymphoma (± villous lymphocytes)	Splenic marginal zone lymphoma (± villous lymphocytes)	9689 / 3
Hairy cell leukaemia	Hairy cell leukaemia	Hairy cell leukaemia	9940 / 3
Plasmacytic lymphoma (Plasmacytoma)	Plasmacytoma / Plasma cell myeloma	Plasma cell neoplasms Plasma cell myeloma Solitary plasmacytoma of bone Extraosseous plasmacytoma	 9732 / 3 9731 / 3 9734 / 3
	Marginal zone B-cell lymphoma, extranodal (MALT-type ± monocytoid B cells)	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699 / 3
Monocytoid B-cell lymphoma	*Marginal zone B-cell lymphoma, nodal (± monocytoid B cells)*	Nodal marginal zone B-cell lymphoma (± monocytoid cells)	9699 / 3
	Follicle centre lymphoma, follicular	Follicular lymphoma	9690 / 3
Centroblastic-centrocytic lymphoma, follicular, follicular and diffuse – with an increased number of centroblasts Centroblastic lymphoma, follicular	*Grade I* *Grade II* *Grade III* *Grade III*	Grade 1 Grade 2 Grade 3a Grade 3b	
Centroblastic-centrocytic lymphoma, diffuse	*Follicle centre lymphoma, diffuse, small cell*	Diffuse follicle centre lymphoma	
Centrocytic (mantle cell) lymphoma Centroblastic lymphoma, centrocytoid	Mantle cell lymphoma	Mantle cell lymphoma	9673 /3
Centroblastic lymphoma, diffuse B immunoblastic lymphoma B-cell large anaplastic lymphoma	Diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma (variants) centroblastic immunoblastic anaplastic T-cell / histiocyte rich plasmablastic with expression of full length ALK (IgA+)	9680 / 3
	DLBCL subtype: Primary mediastinal (thymic) large B-cell lymphoma	Mediastinal (thymic) large B-cell lymphoma	9679 / 3
Angio-endotheliotropic (intravascular) lymphoma	Diffuse large B-cell lymphoma	Intravascular large B-cell lymphoma	9680 / 3
	Diffuse large B-cell lymphoma	Primary effusion lymphoma	9678 / 3
Burkitt lymphoma (BL)	Burkitt's lymphoma	Burkitt lymphoma	9687 / 3
BL with intracytoplasmic immunoglobulin	*DLBCL subtype: High-grade B-cell lymphoma, Burkitt-like*	BL with plasmacytoid differentiation atypical BL / Burkitt-like	
	Burkitt leukaemia	Burkitt leukaemia	9826 / 3
		B-cell proliferations of uncertain malignant potential	
Lymphomatoid granulomatosis (Liebow)		Lymphomatoid granulomatosis	9766 / 1
		Post-transplant lymphoproliferative disorder, polymorphic	9970 / 1

Kiel (updated) 1992	REAL 1994	WHO 2001	ICD-O code
T-cell lymphomas	**T-cell and putative NK-cell neoplasms**	**T-cell and NK-cell neoplasms**	
	Precursor T-cell neoplasm	**Precursor T-cell and NK-cell neoplasms**	
Acute lymphoblastic T-cell leukaemia	Precursor T lymphoblastic leukaemia /	Precursor T lymphoblastic leukaemia /	9837 / 3
T lymphoblastic lymphoma	lymphoma	lymphoma	9729 / 3
		Blastic NK-cell lymphoma	9727 / 3
	Peripheral T-cell and NK-cell neoplasms	**Mature T-cell and NK-cell neoplasms**	
T-cell prolymphocytic leukaemia / T-cell chronic lymphocytic leukaemia (knobby-type)	T-cell prolymphocytic leukaemia / T-cell chronic lymphocytic leukaemia	T-cell prolymphocytic leukaemia	9834 /3
T-cell chronic lymphocytic leukaemia (azurophilic-type)	Large granular lymphocyte leukaemia (LGL) of T-cell type	T-cell large granular lymphocytic leukaemia	9831 / 3
	Large granular lymphocyte leukaemia (LGL) of NK-cell type	Aggressive NK-cell leukaemia	9948 / 3
T-cell lymphoma, small cell type, pleomorphic medium and large cell type (HTLV-1$^+$)	Adult T-cell lymphoma / leukaemia (HTLV-1$^+$)	Adult T-cell leukaemia / lymphoma	9827 / 3
	Angiocentric T-cell lymphoma	Extranodal NK-/T-cell lymphoma, nasal type	9719 / 3
	Intestinal T-cell lymphoma (± enteropathy)	Enteropathy-type T-cell lymphoma	9717 / 3
	Hepatosplenic γδ T-cell lymphoma	Hepatosplenic T-cell lymphoma	9716 / 3
	Subcutaneous panniculitic T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	9708 / 3
Small cell cerebriform (mycosis fungoides / Sézary syndrome)	Mycosis fungoides	Mycosis fungoides	9700 / 3
	Sézary syndrome	Sézary syndrome	9701 / 3
	Primary cutaneous anaplastic large cell (CD30$^+$) lymphoma	Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	9718 / 3
Pleomorphic small, medium-sized and large T-cell lymphoma	Peripheral T-cell lymphoma, unspecified	Peripheral T-cell lymphoma, unspecified	9702 / 3
T-zone lymphoma		T-zone variant	
Lymphoepithelioid (Lennert's) lymphoma		Lymphoepithelioid cell variant (Lennert lymphoma)	
T immunoblastic lymphoma			
Angioimmunoblastic (AILD, LgX-type)	Angioimmunoblastic T-cell lymphoma	Angioimmunoblastic T-cell lymphoma	9705 / 3
T-cell large anaplastic (Ki-1$^+$) lymphoma	Anaplastic large cell lymphoma, CD30$^+$ (T$^-$/null-cell types)	Anaplastic large cell lymphoma	9714 / 3
		T-cell proliferation of uncertain malignant potential	
		Lymphomatoid papulosis	9718 / 1
Not listed in the Kiel classification	**Hodgkin's disease**	**Hodgkin lymphoma**	
	Lymphocyte predominance (Paragranuloma)	Nodular lymphocyte predominant Hodgkin lymphoma	9659 / 3
	Classical Hodgkin's disease	**Classical Hodgkin lymphoma**	9650 / 3
	Nodular sclerosis	Nodular sclerosis	9663 / 3
	Lymphocyte-rich classical HD	Lymphocyte-rich	9651 / 3
	Mixed cellularity	Mixed cellularity	9652 / 3
	Lymphocyte depletion	Lymphocyte-depleted	9653 / 3

Introduction

Classification of diseases is one of the most straightforward analytical endeavours in traditional medicine which mirrors temporary knowledge on a specific subject. In the field of malignant lymphomas an iterative renewal of classification seems to be inevitable, having regard to the continuous accumulation of new insight into their biology. Thus, proposals for new classifications should be understood as a compulsory step-by-step update process reflected in a constant adaptation of nomenclature, inasmuch as more appropriate terms which better contribute to newly discovered characteristics replace old names which have lost their meaning.

Modern technologies yield new criteria which fuel new concepts to interpret old entities. Thus,

histomorphological criteria initiated the Rappaport classification's subdivision into diffusely growing tumours and others with a nodular growth pattern [1]. Cytomorphological features fuelled the concept of histological tumour grading into low grade and high grade malignancies, as proposed in the Kiel classification [2, 3]. Immunophenotypic profiling laid the foundation for both the Lukes & Collins classification [4] and the Kiel classification [2, 3], where lymphoma subtypes and clinicopathological entities respectively were understood in functional terms on the basis of the concept of histiogenetically defined tumour cells and their physiological counterparts respectively. With prognostic tumour grouping according to the aggressiveness of diseases into low, intermediate, and high grade malignancies, a clinical approach was adopted in the International Working Formulation (IWF) [5] which was actually meant to serve as a translational tool between pre-existing classifications rather than as a classification of its own. Finally, a synthesis of morphological, phenotypic, genotypic, and clinical characteristics is mandatory for the diagnosis of disease entities, morphological variants and clinical subtypes as defined in the REAL [6, 7] and WHO [8] classifications.

Thus, the 2001 WHO classification of lymphoid tumours (table 1) is the latest, but definitely not the last attempt at a consensus among clinicians and pathologists on the definition of "*real*" entities and their diagnostic criteria. However, since it is based on agreement between 51 experts worldwide, the WHO classification conveys the best international acceptance ever achieved. It fulfils the requirements of a modern classification, since it is conceptually and scientifically accurate, flexible and easily modified, understandable in its nomenclature and clinically useful for therapeutic trials. However, the diagnostic process, involving as it does today an increasingly complex multivariate genetically biased approach, is no longer practicable in every kind of non-universal laboratory, since it requires facilities far exceeding the simple repertoire of daily tools at hand.

B-cell neoplasms

Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), B-cell prolymphocytic leukaemia (B-PLL) and lymphoplasmacytic lymphoma (LPL) (table 2)

The WHO classification separates *B-cell prolymphocytic leukaemia* from chronic lymphocytic leukaemia/small lymphocytic lymphoma and, as in the Kiel classification, defines it as a disease entity of its own. Lymphoplasmacytic lymphoma (LPL), which was named lymphoplasma*cytoid* lymphoma (immunocytoma) in the REAL classification and corresponds to the Kiel classification's immunocytoma, lymphoplasma*cytic* type, shows a considerable overlap with marginal zone B-cell lymphoma. As in the REAL classification, LPL is distinguished from lymphocytic lymphomas with or without plasmacytoid differentiation.

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), nodal marginal zone B-cell lymphoma (± monocytoid cells), and splenic marginal zone lymphoma (± villous lymphocytes) (table 3)

For these three types of lymphoma, for which the term *marginal zone* is used, the WHO classification is conceptually identical with the REAL classification, with the sole difference that nodal marginal zone B-cell lymphoma and splenic marginal zone lymphoma are no longer provisional entities. Thus, extranodal marginal zone B-cell lymphomas (MALT lymphomas) and nodal marginal zone B-cell lymphomas are very closely related tumours, both recognised as being derived from post germinal centre marginal zone B cells (memory B cells). However, splenic marginal zone lymphoma (SMZL) with or without villous lymphocytes differs markedly in its clinical manifestation, morphological presentation and phenotypic and genotypic profile, originating from a post germinal centre B cell of unknown differentiation state [9–12].

Follicular lymphoma

The histogenetically coined term *follicle centre lymphoma, follicular* as proposed in the REAL classification and preceded by *centroblastic-centrocytic lymphoma* in the original Kiel classification, has been replaced by the pattern-descriptive term *follicular lymphoma (FL)*. The growth pattern of these tumours is usually follicular (follicularity >75%) and less often follicular and diffuse (follicularity 25–75%) or minimally follicular (follicularity <25%). While semantically the WHO classification emphasises *follicularity* as the hallmark feature, it also recognises more variable characteristics such as interfollicular tumour components, marginal zone differentiation, plasmacytoid differentiation with signet ring cells, or floral germinal centres as previously described by others [13–16]. A provisional histological grading system without specific criteria, as used in the REAL classification, has been standardised in the WHO classification on the strength of Berard's criteria [17]. On the basis of counts of centroblasts (CB) in 10 neoplastic follicles in 40× high power field magnification (hpf), FL are subgrouped into Grade 1 (0–5 CB/hpf), Grade 2 (6–15 CB/hpf), and Grade 3 (>15 CB/hpf) tumours. Among Grade 3 FL, the

Table 2

Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL / SLL*), B-cell prolymphocytic leukaemia (B-PLL), and lymphoplasmacytic lymphoma (LPL) in the WHO classification.

Diagnostic criteria	CLL/SLL*	B-PLL	LPL
Clinics			
Age	older adults	elderly	older adults
Infiltration and presentation	**bone marrow,** lymphadenopathy, spleen, and extranodal organs **leukaemic**/aleukaemic* Waldenström	**splenomegaly, leukaemic lymphocytosis** (100×10^9/l), bone marrow	lymphadenopathy, bone marrow, spleen (leukaemic) **Waldenström**
Course	indolent incurable disease	aggressive incurable disease	indolent incurable disease
Morphology			
Pattern	**pseudofollicular,** diffuse	diffuse, interfollicular	diffuse, interfollicular
Cytology	**lymphocytes,** prolymphocytes, paraimmunoblasts	**prolymphocytes** (>55% of lymphoid cells in peripheral blood) lymphocytes, paraimmunoblasts	**lymphocytes, plasmacytoid lymphocytes, plasma cells,** immunoblasts
Variants	atypical CLL		
	CLL with increased prolymphocytes		
	CLL with plasmacytoid differentiation		
	μ-heavy chain disease		γ-heavy chain disease
Phenotype			
Positive		($CD20^+$) $CD79a^+$ sIg^+	
	$CD5^+$ $CD23^+$ $CD43^+$	**$CD5^{+/-}$ $CD23^-$**	**$CD5^-$ $CD23^-$ $CD43^{+/-}$ cIg^+**
Negative		$CD10^-$ $CD103^-$ bcl-6^- $CND\text{-}1^-$	
Genotype			
V_H	**50–60% mutated**	?	mutated
	40–50% non-mutated	?	
Translocations and chromosomal aberrations	**trisomy 12**		***t(9;14) (p13;q32)*** →
	13q aberrations		rearrangement of PAX-5 gene
	del 11q22–23		→ encoding for B-cell specific
	p53 abnormalities	**p53 abnormalities**	activator protein (BSAP)

WHO classification additionally distinguishes those with solid sheets of centroblasts (grade 3b) from those in which centroblasts are intermingled with centrocytes (grade 3a). Small areas of grade 3 FL in otherwise grade 1 or grade 2 FL are diagnosed separately, with an approximate quantification of both tumour components. Likewise, two separate diagnoses are given in cases of FL with considerable diffuse centroblastic areas, namely *follicular lymphoma and diffuse large B-cell lymphoma*. Nuclear *bcl-6* protein expression and the finding of ongoing somatic hypermutations of the immunoglobulin heavy chain variable region (Ig-V_H) genes substantiate the phenotypic and genotypic characterisation of FL. The REAL classification's provisional subtype *follicle centre lymphoma, diffuse, predominantly small cell* is also recognised in the WHO classification as *diffuse follicle centre lymphoma*, representing the extremely rare purely diffuse variant of FL.

Furthermore, the WHO classification distinguishes *cutaneous follicle centre lymphoma*, which, by definition, originates in the skin and stays localised there with no other manifestation for at least 6 months. It is mainly located in the head and neck region or the trunk, rarely disseminates, and is sensitive to local radiotherapy [18]. Absent *bcl-2* immunoreactivity is a common, albeit variable feature [19]. Predictive factors in FL, other than cutaneous origin, are histological grading, grade 1 and 2 being indolent but mainly incurable and grade 3 aggressive but potentially curable tumours, adriamycin containing treatment in grade 3 FL, and serum LDH level.

Diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, and Burkitt lymphoma

Diffuse large B-cell lymphoma (DLBCL), as a term, was coined by the ILSG in proposing the REAL classification. Thus, clinicopathological entities such as diffuse centroblastic lymphoma of polymorphic, monomorphic and multilobated subtype, immunoblastic lymphoma, and B-cell anaplastic lymphoma, as previously defined in the Kiel classification, were lumped together in the DLBCL category. The authors believed that, in view of inadequate knowledge of the biology of these tumours, a purely morphological subclassification with no specific phenotypic and/or genotypic background was useless and not sufficiently reproducible. Some cases with morphological features intermediate between DLBCL, centroblastic variant and Burkitt's lymphoma, expression of *bcl-2* protein and *bcl-2* rearrangement in some

Table 3

Extranodal marginal zone B-cell lymphoma (MALT lymphoma), nodal marginal B-cell lymphoma, and spenic marginal zone lymphoma in the WHO classification.

Diagnostic criteria	Extranodal marginal zone B-cell lymphoma (MALT)	Nodal marginal zone B-cell lymphoma	Splenic marginal zone lymphoma (SMZL)
Clinics			
Presentation	**stomach** lungs head and neck occular adnexae skin, thyroid breast, parotid gland ... tissue-specific homing pattern	localized/generalized lymphadenopathy, in $^1/_3$ of the cases in combi nation with a MALT lymphoma	**spleen** and hilar lymph nodes, no generalized lymphadenopathy
Stage	IE and IIE > IIIE and IVE	I, II, III, IV	IIIE and IVE > IE and IIE
– Bone marrow	+	++	+++
– Leukaemic	(+)	(+)	+++ **villous lymphocytes**
Morphology			
Tumour cells	marginal zone (centrocyte-like) B-cells, monocytoid B-cells and/or small B-lymphocytes with plasma cell differentiation and intermingled blasts of immunoblast/centroblast type		biphasic: central small lympho cytes in the mantle zone and peripheral marginal zone cells in the marginal zone
Special features	**lymphoepithelial lesions**	**monocytoid B-cells**	**bone marrow: intrasinusoidal**
	active residual lymph follicles		
	high grade transformation / progression into diffuse large B-cell lymphoma (DLBCL)		
Phenotype			
positive		$CD20^+$ $CD79a^+$	
	IgM^+ **$CD43^{+/-}$ $bcl\text{-}10^{-/+}$**	IgM^+ **$IgD^{-/+}$**	**IgM/IgD^+ $DBA44^{+/-}$ $CD103^-$**
negative	$CD5^-$ $CD10^-$ $CD23^-$ **IgD^-**	$CD5^-$ $CD10^-$ $CD23^-$ **$CD43^-$**	$CD5^-$ $CD10^-$ $CD23^-$ **$CD43^-$**
Genotype			
V_H	somatic hypermutations		
translocations and chromosomal aberrations	***t(1;14) (p22;q32)*** → *nuclear bcl-10* expression		
	t(11;18) (q21;q21) *API2–MLT fusion transcript*		
	trisomy 3		**allelic loss of 7q (q21–32)**

30% but no *c-myc* rearrangement, corresponding in part to Burkitt lymphomas with intracytoplasmic immunoglobulin as defined in the Kiel classification, were provisionally subtyped as *high-grade B-cell lymphoma, Burkitt-like*. Additionally, *primary mediastinal (thymic) large B-cell lymphoma* was classified as a clinically distinctive subtype of DLBCL.

DLBCL in terms of the WHO classification encompasses a group of cytologically heterogeneous tumours composed of large transformed lymphoid cells. Morphologically they are subdivided into *centroblastic*, *immunoblastic*, *T-cell/histiocyte rich* and *anaplastic* variants of DLBCL. However, distinction of these variants has met with poor intra- and interobserver reproducibility, *inter alia* because, with rare exceptions, phenotypic and genotypic features do not reveal discriminating profiles. Thus, it is optional for the pathologist to give the diagnosis of a DLBCL or more specifically of a morphological variant. In the WHO classification the category of DLBCL comprises, as a new feature, two other variants with distinctive phenotypes. The *plasmablastic variant* as usually present in the oral cavity in an HIV^+ setting is positive for EBV and plasma cell antigens, but negative for CD45 and CD20. The *variant with expression of full-length ALK*, as described by Delsol [20], has an immunoblastic morphology with mainly plasmablastic differentiation and expresses EMA, CD45, IgA, ALK and plasma cell antigens but no B- and T-cell antigens except CD4 and CD57. Unlike anaplastic large cell lymphoma, it has no *t(2;5)* translocation, no NPM-ALK hybrid gene, and no NPM-ALK fusion transcript (see below).

Clinically, DLBCL follow an aggressive course but respond very variously to treatment in that only some 40% can be cured. Looking for prognostically discriminating features Aliasadeh *et al.* [21] followed a genetic approach. They functionally classified many hundreds of genes by means of DNA microarrays and established an outcome predictor score. Thus, on the basis of different gene expression signatures suggestive of different stages of B-cell differentiation, two major subtypes with significantly different clinical outcomes were distinguished, namely the prognostically favourable *G*erminal *C*entre *B*-cell-like (GCB) DLBCL and the unfavourable *A*ctivated *B-C*ell-like (ABC) DLBCL. Clinically distinctive subtypes such as mediastinal (thymic), intravascular and primary effusion large B-cell lymphomas are excluded from the DLBCL category and recognised as separate disease entities.

Mediastinal (thymic) large B-cell lymphoma (MLBCL) was also recognised and well described in the REAL classification. It originates from pu-

tative thymic B-cells (asteroid cells) or post-germinal centre cells of very late pre-plasmacyte B-cell differentiation. Phenotypically it can be distinguished from Hodgkin lymphoma by the expression of CD45, Bob-1 and Oct-2, *MAL* and CD23 and the absence of immunoreactivity for CD15. Specific genotypic aberrations in MLBCL comprise *REL* gene amplification, gains of chromosome 9, *MAL* gene overexpression and *bcl-6* mutations [22].

Intravascular large B-cell lymphoma is a very rare type of B-cell lymphoma originating from transformed peripheral B-cells and presenting as an intravascular accumulation of B-blasts ($CD20^+$). It is widely disseminated at extranodal sites and the clinical symptoms are related to occlusions of small vessels in the relevant organ. The response to therapy is very poor and the prognosis is extremely unfavourable [23].

Primary effusion lymphoma originates from post-germinal centre B-cells and manifests itself as serous effusions in body cavities, usually in an HIV^+ setting associated with HHV8/KSHV infections, with or without Kaposi's sarcoma or multicentric Castleman's disease. The prognosis is extremely unfavourable. The tumour cells of centroblastic, immunoblastic, or anaplastic morphology express CD45, plasma cell markers and HHV8/KSHV-associated latent protein but no pan-B-cell antigens and no immunoglobulins [24].

Burkitt lymphoma (BL) is a highly aggressive tumour most typically of extranodal origin which in very rare cases presents as acute leukaemia. In spite of its unfavourable natural history it is highly sensitive to aggressive chemotherapy and is thus in fact curable in most cases. Epidemiologically the WHO classification distinguishes three clinical variants, viz. *endemic BL* of equatorial Africa and Papua New Guinea, *sporadic BL* with worldwide occurrence, and the *immunodeficiency-associated BL* usually found in an HIV^+ setting. These variants are markedly heterogeneous in their biology, i.e. the pathogenetic impact of Epstein-Barr virus (EBV) infections, clinical presentation, i.e. site of origin, and morphological subtypes such as *classical BL* representing endemic and sporadic variants and *BL with plasmacytoid differentiation* and *atypical BL/Burkitt-like* subtypes, both found chiefly in combination with HIV infection. Compared to classical BL, variants with plasmacytoid differentiation and atypical BL/Burkitt-like show more morphological atypias and considerable pleomorphism of nuclear shape and size. They may correspond in part to the provisional entity of high-grade B-cell lymphoma, Burkitt-like as defined in the REAL classification. Phenotypically, BL express B-cell antigens, CD10, and *bcl-6* protein and are negative for CD5, CD23 and TdT. The proliferation index as measured by nuclear immunoreactivity with Mib-1 (Ki67) is higher than 95%. Monotypic *cytoplasmic* Ig is found in BL with plasmacytoid differentiation. Burkitt leukaemias exhibit a mature B-cell phenotype positive for CD45 and B-cell antigens and negative for CD34 and TdT. On the basis of morphological and immunological criteria alone, differential diagnosis between BL and DLBCL leaves a considerable grey zone open. Thus clinical data, such as extranodal tumour bulk, high serum LDH and tumour lysis syndrome are very valuable diagnostic parameters. In the WHO classification, however, *c-myc* rearrangements, due to *t(8;14)* rather than to *t(2;8)* or *t(8;22)* translocation is an invariable genetic feature of BL. Originating from germinal centre B-cells, BL shows ongoing somatic hypermutations of the Ig-V_H genes.

Lymphomatoid granulomatosis and post-transplant lymphoproliferative disorder

In addition to B-cell neoplasms the WHO classification encompasses two types of B-cell proliferation of uncertain malignant potential, which are not contained in the REAL classification.

Lymphomatoid granulomatosis, as previously described by Liebow [25], is an EBV-driven lymphoproliferative disorder chiefly found in patients with underlying immunodeficiency caused by HIV infection, Wiscott-Aldrich's syndrome or the X-linked lymphoproliferative syndrome. It is localised in extranodal organs, most typically in the lungs, and the clinical symptoms are, apart from constitutional symptoms, related to the relevant organ infiltration. It shows an angiocentric and angiodestructive growth pattern with infarctious lesions and is to be distinguished from extranodal NK-/T-cell lymphoma, nasal type (see below). Morphologically the infiltrate is composed of EBV-positive atypical blasts of B-cell phenotype ($CD20^+$) admixed with numerically predominant reactive T-lymphocytes, plasma cells and histiocytes. Depending on the varying proportions of these large B cells and the extent of necrosis, lymphomatoid granulomatosis varies in histological grade (I–III) and clinical aggressiveness. While most cases of grade II and grade III disease exhibit clonally rearranged immunoglobulin genes, grade III cases display the morphology of overt B-cell lymphoma, which the WHO classification considers a subtype of DLBCL.

Post-transplant lymphoproliferative disorder (PTLD) encompasses a continuous spectrum of largely EBV-infection-associated lymphoid proliferations, mainly of host rather than of donor origin and consequently evolving to immunosuppression in recipients of allografts. PTLD are divided into early lesions, polymorphic PTLD, monomorphic PTLD and Hodgkin lymphoma, including Hodgkin-like PTLD. *Early lesions*, i.e. reactive plasmacytic hyperplasia and infectious mononucleosis-like lesions, are characterised morphologically by at least partial architectural preservation of infiltrated tissues, phenotypically by polyclonal Ig expression and LMP-EBV positivity, and genotypically by a germline Ig configuration. Clinically, they show spontaneous regression with reduction of immunosuppression in most

cases. *Polymorphic PTLD* present morphologically as a tissue-destructive B- and T-cell mixed lymphoproliferation with intermingled atypical, bizarre EBV-positive immunoblasts showing the full range of B-cell maturation to plasma cells, thus resembling the composition of "polymorphic immunocytoma" as described in the original Kiel classification. Phenotypically they express monotypic Ig. Genotypically they nearly always have clonally rearranged Ig genes and EBV genomes. Clinically they may regress but usually progress to monomorphic PTLD. *Monomorphic PTLD* corresponds morphologically, phenotypically and genotypically to overt lymphoma of B-cell subtype rather than of T-cell subtype with clonal Ig profiles and EBV genomes in clonal episomal forms. Some PTLD present as *Hodgkin lymphoma or Hodgkin-like lesions*, similar to methotrexate-related HL or HL in an HIV^+ setting.

T-cell and NK-cell neoplasms

Blastic NK-cell lymphoma

Blastic NK-cell lymphoma is a new entity to the WHO classification not recognised by the REAL classification. It is a clinically aggressive lymphoma with a poor response to treatment protocols, no known racial predilection and no association with EBV infection. Usually a disseminated disease at presentation, it shows infiltration of multiple extranodal sites, preferably the skin, and at least partly represents precursor NK lymphoblastic lymphoma/leukaemia. Because of a phenotypic overlap with other primary cutaneous haematolymphoid neoplasms and a morphological resemblance to lymphoblastic (or myeloblastic) leukaemias, adequate phenotypic ($CD56^+$ $CD4^+$ $CD43^+$ $TdT^{-/+}$ $CD34^{-/+}$ $CD123^+$ $CD3^-$ $CD7^-$ $TIA\text{-}1^-$ $CD68^-$ $CD33^-$) and genotypic (germline configuration of T-cell receptor genes) profiles are mandatory [26, 27].

T-cell prolymphocytic leukaemia

In the WHO classification T-cell prolymphocytic leukaemia (T-PLL) replaces, as a term, the REAL classification's hybrid entity T-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia. T-PLL represents a morphological spectrum of clonal diseases of T-prolymphocytes (and T-lymphocytes), including a small cell variant (20%) and a cerebriform or Sézary cell-like variant (5%) [28, 29]. These variants of T-PLL may in part correspond to some cases of T-cell chronic lymphocytic leukaemia (T-CLL) of knobby type (and of pleomorphic type respectively) as defined in older classifications [2–4], whereas the azurophilic type of T-CLL is covered by T-cell large granular lymphocytic leukaemia [30]. In terms of the Kiel classification, T-PLL and T-CLL can be distinguished only on imprints and peripheral blood smears, but not on histological sections [3]. Immunologically, T-PLL exhibits a profile of mature T-cells with constant expression of CD7, characteristically variable CD4/CD8 status, and constant negativity for HTLV-1. Clinically, T-PLL presents with hepatosplenomegaly, generalised lymphadenopathy, skin infiltration in 20%, and marked lymphocytosis exceeding 100×10^9/l. It follows an aggressive course showing an encouraging response in cases treated with CD52 monoclonal antibodies (CAMPATH-1H). Terminologically, however, T-CLL no longer figures in the WHO classification.

Extranodal NK-/T-cell lymphoma, nasal type

Renamed according to the new nomenclature, *extranodal NK-/T-cell lymphoma, nasal type* is not an entity new to the WHO classification but is equivalent to the angiocentric (T-cell) lymphoma well defined in the REAL classification. Angiocentricity, angioinvasion, and angiodestruction are histomorphological hallmarks of this cytologically variegated tumour, resulting in vascular occlusions and consequent ischaemic necrosis and ulceration. Involvement of the nasal cavity, being the prototypic extranodal site of origin, may present as midfascial destruction also known by the descriptive term *lethal midline granuloma*. Lymphomatoid granulomatosis, however, may be distinguished immunologically and represents a lymphoproliferative disorder of B-cell lineage. Phenotypically, extranodal NK-/T-cell lymphoma, nasal type most typically exhibits CD2, CD56, EBV, cytotoxic antigens and cytoplasmic CD3, but no surface CD3 and no CD4, CD5, CD8, or CD43. Genotypically, Ig and TcR genes are found to be in germline configuration, whereas EBV genomes present in clonal episomal forms.

Hepatosplenic T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma

These two disease entities, both associated with an immunosuppressive setting, were, under the terms *hepatosplenic γδ T-cell lymphoma* and *subcutaneous panniculitic T-cell lymphoma* respectively, also recognised by the REAL classification, categorised then as provisional subtypes of peripheral T-cell lymphomas, unspecified. The first originates from immature, the latter from mature cytotoxic T-cells, of both γδ- *and* αβ-types. This is why the "γδ"-affix in hepatosplenic T-cell lymphoma is deleted in the WHO classification nomenclature.

Anaplastic large cell lymphoma, primary cutaneous anaplastic large cell lymphoma (C-ALCL), and lymphomatoid papulosis

Anaplastic large cell lymphoma is the prototype of a lymphoid neoplasm which has been named and renamed according to changing interpretations, initially on the basis of morphological and phenotypic and later of genotypic features and yet may still not be ultimately defined! In 1985, when Stein *et al.* incubated a series of morphologically unclassifiable tumours with the Hodgkin's disease-associated antibody Ki-1 (CD30), it was found that there was a new Ki-1 positive large cell lymphoid neoplasm which had not been recognised before [31]. On the basis of cytologically large- to giant-sized tumour cells, which could not then be correlated with any known physiological or neoplastic lymphoid cells, the morphological term *large cell anaplastic lymphoma (LCAL)* was coined. When one year later Kadin *et al.* [32] proposed the alternative immunohistological term *Ki-1 lymphoma*, it was popular among clinicians but strongly disliked by pathologists. Thus, the phenotypic feature of Ki-1 immunoreactivity is, on the one hand, not specific for LCAL, being also found in many other subtypes of lymphoma of B-cell and T-cell lineage and even in non-lymphoid tumours, i.e. embryonal carcinoma; on the other hand, Ki-1 is not invariably exhibited in LCAL, leading to nonsense casuistics of "*Ki-1 negative Ki-1 lymphoma*". However, the morphologically based terminology also became problematic, when Kinney *et al* [33] described a small-cell-predominant variant of primary Ki-1 $(CD30)^+$ T-cell lymphoma, resulting in a semantically paradoxical "*large cell anaplastic lymphoma*, *small cell variant*".

When the ILSG proclaimed the REAL classification, the term *anaplastic large cell lymphoma (ALCL)* was restricted to T-cell and null-cell neoplasms, both of which, irrespective of different antigenic profiles concerning the expression of T-cell markers, showed clonally rearranged T-cell receptor genes of γ or β type in about 90% of cases. However, in contrast to the Kiel classification, anaplastic tumours of B-cell phenotype were separated and put into the diffuse large B-cell lymphoma group (see above). In the range of a morphological spectrum, classical ALCL was distinguished from a *small cell variant* and a *lymphohistiocytic variant*, whereas *ALCL Hodgkin's-like* [34], as an entity, remained provisional. Clinically, the REAL classification distinguished between two distinct forms of primary ALCL: a systemic form involving lymph nodes and extranodal sites and a primary cutaneous form, the second of which remained provisional, showing a considerable clinical, morphological, phenotypic, and genotypic overlap with type-A lymphomatoid papulosis [35]. However, primary cutaneous forms were distinct from systemic forms: phenotypically by immunoreactivity with the cutaneous lymphocyte antigen (CLA, HECA-452) and negativity for EMA, and genotypically by the absence of *t(2;5)* translocation.

In the WHO classification ALCL, a tumour originating from activated mature cytotoxic T-cells, is defined as a neoplasm composed of large pleomorphic cells often with horseshoe- or kidney-shaped nuclei (so called hallmark cells) with abundant cytoplasm, strong CD30 expression on the cell membrane or the Golgi region in the great majority of tumour cells, and no expression of B-cell antigens [36]. The WHO classification distinguishes three subtypes of ALCL: (1) *systemic ALCL*, ALK^+, typically presenting as advanced stage disease in young men, highly sensitive to chemotherapy and with a favourable prognosis (5-year (y) overall survival (os): 80%; 10-y os: 70–90%); (2) systemic *ALCL*, ALK^-, affecting older patients, located less often at extranodal sites and with a markedly less favourable prognosis (5-y os: 40%); and (3) *cutaneous ALCL*, by definition a localised disease in the skin over 6 months [18], highly sensitive to local treatment and with an excellent prognosis (10-y os: >90%). Since cutaneous ALCL may represent a continuous spectrum with type A lymphomatoid papulosis, both of these conditions are subsumed in the WHO classification under the term *primary cutaneous CD30-positive T-cell lymphoproliferative disorders.* Morphologically, *lymphohistiocytic*, *small cell*, *giant cell rich*, *signet ring cell-like*, *sarcomatoid*, *neutrophilic*, and *eosinophilic variants* are distinguished from *ALCL*, *common type*, whereas ALCL Hodgkin's-like, recognised as a provisional entity in the REAL classification, no longer figures in the WHO classification. Thus, most such cases could be identified phenotypically as Hodgkin lymphomas characterised by expression of CD15, LMP-EBV and, in part, of B-cell markers, while phenotypic profiles, such as $CD30^+/CD15^-$, $LMP\text{-}EBV^-$, EMA^+, $CD45(^+)$, $CD3^{-/+}$, $CD4^+/CD8^-$, $CD2^+$, $CD43^+$, $TIA\text{-}1^+$, Granzyme B^+, $Perforin^+$, $Clusterin^+$, $ALK^{+/-}$, $CD56^{-/+}$, $CD20^-$, $CD79a^-$, and $BSAP^-$ characterise ALCL, leaving out a few cases only of so-called *grey zone lymphoma*. However, the molecular hallmark features found in the majority of systemic ALCL cases, but not in primary cutaneous forms, are genetic alterations of the anaplastic lymphoma kinase (ALK) locus on chromosome 2. In 70–80% of cases, the *t(2;5)* translocation juxtaposes parts of the nucleophosmin (NPM) gene (5q35) to the ALK gene (2p23), bringing the ALK gene under the control of the NPM promotor. The formation of this NPM-ALK hybrid gene results in continuous activation of the NPM-ALK fusion transcript and overexpression of the chimeric NPM-ALK protein (p80). Alternative genetic aberrations, such as *t(1;2)*, *t(2;3)*, *Inv2*, and *t(2;17)* are less often found, resulting in the formation of variant TPM3-ALK (tropomyosin 3), TFG-ALK (Trk-fusion gene), ATIC-ALK (pur-H gene), and CLTC-ALK (clathrin heavy chain) hybrid genes, fusion transcripts and chimeric proteins respectively [36]. However,

variable genetic alterations of the ALK locus and heterogeneous phenotypic ALK profiles may finally cast doubt on whether ALCL is ultimately the correct term.

Hodgkin lymphomas

Lymphocyte-rich classical Hodgkin lymphoma

In the WHO classification Hodgkin's disease, as a term, is replaced by Hodgkin lymphoma. *The lymphocyte-rich subtype of classical Hodgkin lymphoma*, as recognised in the REAL classification, is no longer provisional but a disease entity corresponding in its nodular form to follicular Hodgkin's disease as first described by Ashton-Key *et al.* [37]. However, lymphocyte-rich classical Hodgkin lymphoma needs to be clearly distinguished from nodular lymphocyte predominant Hodgkin lymphoma, which is identical to nodular paragranuloma in the REAL classification.

We thank Professor Robert Maurer for his helpful comments and for kindly reviewing the manuscript.

Correspondence:
Sergio B Cogliatti, MD
Chairman of the SAKK Pathology Reference Centre for Malignant Lymphomas
Department of Pathology
Cantonal Hospital St. Gallen
Rorschacherstrasse 95
CH-9007 St.Gallen
E-Mail: sergio.cogliatti@kssg.ch

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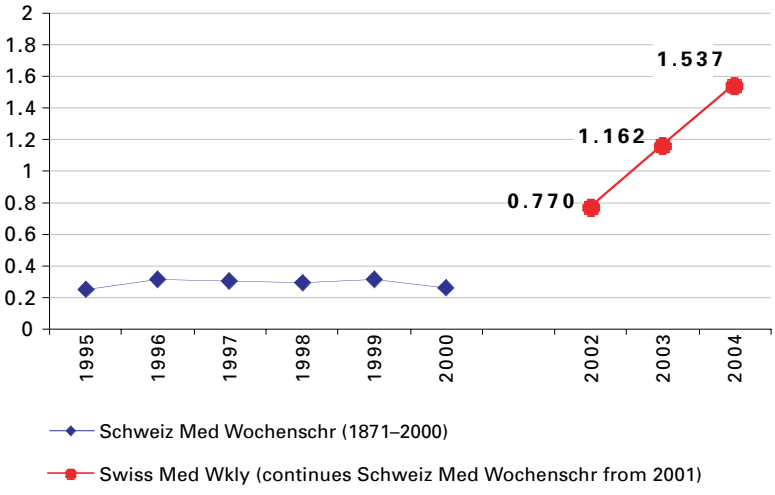

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