

CHAPTER 3 CLASSIFICATION

3.1 Introduction

Accurate diagnosis underpins lymphoma management. Historically, competing lymphoma classifications have been a source of frustration to pathologists, clinicians and epidemiologists alike. Thus the 1994 publication of the International Lymphoma Study Group's classification, the Revised European-American Lymphoma (REAL) classification¹ marked a watershed in the field of lymphoma diagnosis and management. Its successor, the 2001 WHO classification², is based on the principles of the REAL classification, but with further consensus achieved on some of the diagnostic categories, and with consideration of advice from a clinical advisory committee.³ This classification was achieved with international consensus among expert haematopathologists and is the classification adopted and promoted in these guidelines. As in the REAL scheme, the WHO classification identifies specific disease entities defined not only by morphology, but also by considering the immunophenotype, genetics, and clinical features typical of each entity.

While some diseases may be recognisable with a high (but not absolute) degree of certainty on the basis of morphology alone (e.g. follicular lymphoma), most will require immunophenotyping and/or genotyping for accurate classification. Therefore, laboratories must be able to perform, or at least have access to, immunophenotyping and molecular techniques. The relative importance of each of these parameters in the diagnostic process varies according to each lymphoma.

Particularly in the case of T- and NK-cell lymphomas, the clinical setting and site (nodal versus extranodal) are often more important than morphology in establishing the diagnosis. The pathologist plays a key role not only in establishing the correct diagnosis, but also in ensuring that biopsy material is triaged appropriately. Further ancillary studies should these be selected as appropriate to the individual case.

It is emphasised that not all tests are necessarily required in every case.

3.2 Taxonomic structure

The WHO classification considers lymphoproliferative disorders under three broad groupings of *B-cell* neoplasms, *T-cell and NK-cell* neoplasms, and *Hodgkin lymphoma*.² The lymphoproliferative disorders (LPD) associated with primary or acquired immunodeficiencies are classified separately within the WHO scheme, and include the post-transplant LPD. The B-cell and T/NK cell neoplasms are stratified into those of precursor cell origin (lymphoblastic lymphoma/leukaemia) and those putatively corresponding to later stages of B- and T-cell ontogeny (peripheral or mature lymphomas). Wherever possible, a postulated cell of origin or stage of lymphoid differentiation is given for each entity. Specific clinicopathologic entities are identified in the scheme, and are grouped according to whether they present as mainly disseminated/leukemic disease, as primary extranodal disease, or predominantly as node-based lymphomas. As many factors contribute to the clinical behaviour of any particular lymphoma, histological grading and clinical groupings do not form part of the WHO classification. Indeed, the WHO Clinical Advisory Committee recommended against any clinical groupings.³ *The onus is therefore on the clinician and pathologist to be familiar with the morphological and clinical spectrum within each diagnostic category to determine therapy and predict outcome.*

In the treatment of lymphoma however, the various WHO categories fall into distinct clinical groups eg. low grade, aggressive and high grade lymphomas (see Table 3.1). These provide the framework for discussion about the management of lymphoma in these guidelines.

3.3 Validation of the WHO scheme

An international clinical evaluation and validation study of the REAL classification has been carried out by the Non-Hodgkin's Lymphoma Classification Project.^{4,5} By extension, the conclusions can reasonably be applied to the WHO classification. This study established clearly that the REAL classification enabled high diagnostic accuracy (>95% for cases with adequate materials) and had high interobserver reproducibility among expert haematopathologists (>85%) for most disease categories, better than for any previous classification system. Diagnostic accuracy is not as good for some categories such as lymphoplasmacytic lymphoma, nodal marginal zone lymphoma, and atypical Burkitt lymphoma, and for grading within follicular lymphoma. The importance of immunophenotyping for some entities was clearly established, and immunophenotyping is essential for diagnosis of T-cell lymphomas. The clinical relevance of immunophenotype has been confirmed in other large studies that confirm that the T-cell phenotype is an independently significant negative prognostic factor.^{6,7} The classification is of clinical relevance, as different entities have significantly different clinical presentations⁵ and survivals^{4,5,8}, and clinical factors such as the International Prognostic Index⁹ were established as critical in determining treatment and outcome in any lymphoma type. Using the REAL classification, good diagnostic concordance has been shown between an academic centre and a community hospital setting¹⁰; discordance occurred for those cases which also accounted for higher interobserver variability between expert haematopathologists. Several studies have now been published establishing the frequency of the various lymphoma subtypes in terms of the REAL/WHO classifications.^{7,11-17} These studies also highlight important geographic differences in the incidence of the various lymphoma types.

3.4 Common forms of lymphoma

While the 36 specific disease entities in the NHL classification (excluding immunodeficiency associated LPD) may at first glance appear overwhelming, it is noteworthy that two entities, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), account for >50% of all NHL. B-cell lymphomas represent greater than 85% of all NHL globally; in Western countries at least, T-NHL accounts for less than 15% of all NHL, and most of these fall into the unspecified category.⁴ Thus a minority of lymphomas encountered in routine practice are likely to need extensive ancillary investigations to establish a firm diagnosis.

3.5 Difficulties in classification

While not specifically alluded to in the WHO classification, but addressed in the earlier REAL classification, a small proportion of lymphomas may be unclassifiable due to an inadequate specimen or histological preservation, inadequate immunophenotyping or genotyping, or simply because some lymphomas defy accurate classification despite adequate diagnostic workup. Such a case should be categorised to the extent that the available data allow, but it should not be forced into a diagnostic category if the minimal criteria needed for a specific diagnosis are not met. For example, such lymphomas might be reported as 'B-cell lymphoma, unclassifiable, likely to be high-grade based on a very high proliferation fraction', or 'B-cell lymphoma, unclassifiable'.

In a very small proportion of lymphomas — 'grey zone' lymphomas — it may not be possible to distinguish definitively between NHL and HL even in the hands of expert haematopathologists, owing to significant morphological and immunophenotypic overlap.¹⁸⁻²⁰ Typically, these cases involve distinction between HD (classical HD, or the diffuse form of lymphocyte predominant HD), and anaplastic large-cell lymphoma, mediastinal large B-cell lymphoma or T-cell-rich B-cell lymphoma. In particular, the relationship between T-cell-rich B-cell lymphoma (especially cases with some nodularity — 'paragranuloma-type') and nodular lymphocyte predominant Hodgkin's disease, is a debated issue given the lack of accepted and consistent criteria by which to make the distinction.²⁰ Some of these grey zone lymphomas may represent true biological transitions between HL and NHL, while others, despite morphological and immunophenotypic overlap, are biologically unrelated.

The WHO classification also does not specifically refer to composite lymphomas, which are defined as the synchronous occurrence of two or more morphologically distinct types of NHL and/or HD occurring in the same lymph node or extranodal tissue²¹ and which may or may not be clonally related.²²⁻²⁴ These may take the form of composite B-cell lymphomas (most common), composite T-cell lymphomas (rare), composite B- and T-cell lymphoma, or composite HD and NHL.^{21,25,26} Histologically discordant lymphomas may also occur synchronously or sequentially at different anatomic sites, and may or may not be clonally related.^{27,28} At least some of these represent progression of one lymphoma into a more aggressive type. For reporting purposes, each lymphoma type forming these composite or discordant lymphomas should be included in the diagnostic report.

3.6 Alternative classifications

Recently, the EORTC have proposed an alternative classification scheme for cutaneous lymphomas²⁹, the authors arguing that particular clinicopathological aspects of cutaneous lymphomas are not adequately conveyed in the WHO scheme. We recommend the use of the WHO classification for all forms of lymphoma while recognising that much of the clinical survival data available in cutaneous lymphoma (DCLWG) have been published using the classification scheme of the European Organisation for Research and Treatment of Cancer (EORTC)²⁹ (see Table 3.1).

Key point

The World Health Organisation (WHO) Classification of Haematological Malignancies is the internationally accepted taxonomy for lymphoproliferative disease and should be fundamental to the classification, diagnosis and management of lymphoproliferative disease.

Table 3.1 WHO lymphoma classification

B-CELL NEOPLASMS

Precursor B-cell neoplasm

Precursor B lymphoblastic leukaemia/lymphoma

Mature B-cell neoplasms

Chronic lymphocytic leukaemia/small lymphocytic lymphoma

B-cell prolymphocytic leukaemia

Lymphoplasmacytic lymphoma

Splenic marginal zone lymphoma

Hairy cell leukaemia

Plasma cell myeloma

Solitary plasmacytoma of bone

Extravascular plasmacytoma

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

Nodal marginal zone B-cell lymphoma

Follicular lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphoma

Mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

Primary effusion lymphoma

Burkitt lymphoma/leukaemia

B-cell proliferations of uncertain malignant potential

Lymphomatoid granulomatosis

Post-transplant lymphoproliferative disorder, polymorphic

T-CELL AND NK-CELL NEOPLASMS

Precursor T-cell neoplasms

Precursor T lymphoblastic leukaemia/lymphoma

Blastic NK cell lymphoma **

Mature T-cell and NK-cell neoplasms

T-cell prolymphocytic leukaemia

T-cell large granular lymphocytic leukaemia

Aggressive NK cell leukaemia

Adult T-cell leukaemia/lymphoma

Extranodal NK/T cell lymphoma, nasal type

Enteropathy-type T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous anaplastic large-cell lymphoma

Peripheral T-cell lymphoma, unspecified

Angioimmunoblastic T-cell lymphoma

Anaplastic large-cell lymphoma

T-cell proliferation of uncertain malignant potential

Lymphomatoid papulosis

HODGKIN LYMPHOMA

Nodular lymphocyte predominant Hodgkin lymphoma

Classical Hodgkin lymphoma

Nodular sclerosis Hodgkin lymphoma

Lymphocyte-rich Hodgkin lymphoma

Mixed cellularity Hodgkin lymphoma

Lymphocyte-depleted Hodgkin lymphoma

Immunodeficiency associated lymphoproliferative disorders

Lymphoproliferative diseases associated with primary immune disorders

Human immunodeficiency virus-related lymphomas

Post-transplant lymphoproliferative disorders

Methotrexate-associated lymphoproliferative disorders

HISTIOCYTIC AND DENDRITIC-CELL NEOPLASMS

Macrophage/histiocytic neoplasm

Histiocytic sarcoma

Dendritic cell neoplasms

Langerhans cell histiocytosis

Langerhans cell sarcoma

Interdigitating dendritic cell sarcoma/tumour

Follicular dendritic cell sarcoma/tumour

Dendritic cell sarcoma, not otherwise specified

MASTOCYTOSIS

Cutaneous mastocytosis

Indolent systemic mastocytosis

Systemic mastocytosis with associated clonal, haematological non-mast cell lineage disease

Aggressive systemic mastocytosis

Mast cell leukaemia

Mast cell sarcoma

Extracutaneous mastocytoma

Note: Table modified to exclude myeloproliferative disorders, myeloid leukaemias and mast cell disease.

*Morphology code of the International Classification of Diseases (ICD-O), third edition. Behaviour is coded /3 for malignant tumours and /1 for lesions of low or uncertain malignant potential.

**Neoplasms of uncertain lineage and stage of differentiation.

3.7 References

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