

CHAPTER 8 DIAGNOSIS AND REPORTING OF LYMPHOPROLIFERATIVE DISEASE

8.1 Introduction

The WHO classification, based as it is on ‘clinicopathological entities’, requires for diagnosis the correlation of diverse types of information (clinical, morphological, immunophenotypic and genotypic).¹ This information is of varying complexity, often assembled from different laboratories, and often containing elements of different diagnostic confidence. Clinical information is a prerequisite for the diagnosis of certain WHO categories, especially cutaneous disease, extranodal lymphomas in general, and various forms of NK-cell and T-cell neoplasia.

The challenge in *diagnosis* is to weigh the relative importance of each piece of diagnostic information against the possible differential diagnoses.

The challenge in *reporting* lymphoproliferative disease is to record concisely the diagnostic findings and WHO diagnosis in such a way that the diagnostic decision-making trails, and areas of uncertainty (if present), are clearly documented.

8.2 Diagnostic difficulties

Two main causes may affect *diagnostic certainty*:

- inadequate or insufficient biopsy material or ancillary tests
- diseases that are intrinsically difficult to classify despite adequate biopsy material and ancillary tests.

8.2.1 Inadequate material or ancillary tests

Morphology remains the keystone of lymphoma diagnosis and the production of a well handled, high-quality H&E section remains the single most important element of accurate lymphoma diagnosis.²⁻⁴

What is an adequate biopsy?

An adequate biopsy is one in which there is material of sufficient quantity and quality; and sufficient ancillary investigations have been performed, to enable a confident and specific WHO diagnosis.

Factors influencing adequacy of materials and ancillary studies

- i Pre-biopsy
 - a Inadequate or misleading clinical information
 - b Inappropriate investigational modality
- ii Biopsy
 - a Inappropriate biopsy site
 - b Sample error
 - i Reactive tissue adjacent to tumour^{5,6}
 - ii Partially involved peripheral lymph node
 - iii Composite disease⁵

- iv Necrosis^{7,8}
- c Insufficient sample⁵
 - i For morphological assessment (e.g. needle core or endoscopic biopsies)
 - ii For ancillary studies
- d Artefact
 - i Crush
 - ii Air drying
 - iii Diathermy
 - iv Nuclear artefact in endoscopic and core biopsies
- iii Post-biopsy (technical, laboratory issues)
 - a Routine processing
 - i Inappropriate fixation
 - ii Laboratory processor errors, or staining artefact^{2,5,6}
 - iii Loss of antigenicity
 - iv Loss of DNA
 - b Immunohistochemistry unsatisfactory
 - c Molecular studies unsatisfactory

8.2.2 Diseases that are difficult to classify despite adequate biopsy material and ancillary tests

There are three categories of such diseases:

- i ‘Atypical lymphoid hyperplasia’
- ii Unclassifiable and ‘grey zone’ lymphomas
- iii Unavailability of a pathologist experienced in haematopathology

‘Atypical lymphoid hyperplasia’

‘Atypical lymphoid hyperplasia’ is a condition in which it is not possible to differentiate between a benign or malignant lymphoproliferative condition (see Figure 8.1).⁹ It is not a true clinicopathological entity and is used as an interim label while further investigation is performed, or while the disease declares itself clinically.¹⁰

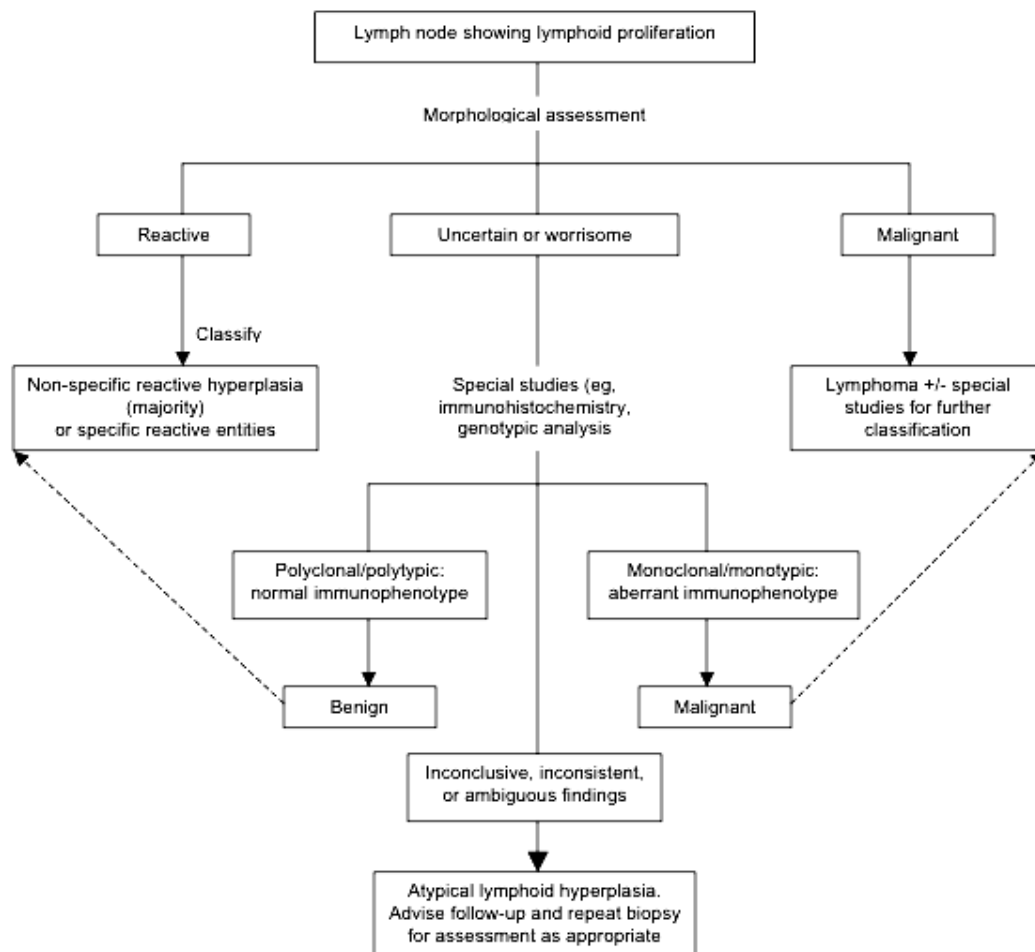
Most studies have indicated a significant risk for the subsequent diagnosis of lymphoma in this group.^{10–12} Once accounting for between 3% and 40% of all lymphoid diagnoses⁹, the term ‘atypical lymphoid hyperplasia’ is now used much less frequently, due to the use of ancillary studies.¹²

Unclassifiable and 'grey zone' lymphomas

This refers to cases in which the disease is clearly a lymphoma but subtyping is difficult due to conflicting or discordant clinical, morphological, immunophenotypic, molecular or genetic findings.^{13,14} Some of these may be variants or new diseases that are not yet recognised within the WHO classification. It is recognised, however, that there may be significant overlap in the morphological and immunophenotypic features of some WHO entities.

The term 'grey zone lymphomas' is generally applied to cases that fall into the differential diagnosis between classical Hodgkin lymphoma (often syncytial), anaplastic large-cell lymphoma, T-cell rich B-cell lymphoma, and mediastinal large B-cell lymphoma.¹⁵

Figure 8.1 Atypical lymphoid hyperplasia



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8.3 Course of action in non-diagnostic cases

8.3.1 Technical causes

In cases where the diagnosis is compromised by insufficient biopsy material, or the quality of the material is compromised by the biopsy technique, this should be clearly stated in the report. On occasion, a poorly fixed sample may be rendered diagnostic by post fixation. In general, however, the

only satisfactory recourse is re-biopsy, preferably by excision biopsy. ***In consulting, there is little value in referring inadequate or unsatisfactory material to another pathologist or institution.***

If there are technical problems with immunophenotyping technique (identified by using appropriate positive and negative control sections), correction may be attempted within the laboratory, or material may be sent to a reference laboratory for staining.

8.3.2 'Atypical lymphoid proliferations' and unclassifiable lymphomas

When good material has been extensively examined and subjected to a full range of ancillary tests with indeterminate results, and a specific lymphoma diagnosis has still not been established, the following courses of action may be considered:

- i Referral of the patient to a unit experienced in haemato-oncology
- ii Referral of the material to an experienced haematopathologist (preferably part of the above clinical unit)
- iii Re-biopsy
- iv Staging procedures
- v Close clinical follow up

Key point

To minimise delays and waste of tissue in diagnostically difficult cases, it may be convenient to refer the material to the pathologist who functions as a member of the multidisciplinary team where the patient will be managed.

8.4 Reporting

8.4.1 Typical report information

A report of lymphoproliferative disease would normally record the following:

- i Patient demographics
- ii Anatomical site of biopsy or organ, whether nodal or extranodal
- iii Type of sample (needle core, endoscopic, incisional, etc.)
- iv Histological diagnosis:
- v WHO classification recommended¹ (see Chapter 3)
Use of alternative classifications is not recommended but should be clearly stated if used.
- vi Composite disease (where relevant)
- vii Tumour progression/transformation (where relevant)
- viii Statement of diagnostic certainty (see Section 8.3.3)
- ix Reasons for any uncertainty (see Section 8.2)

- x Grading (where relevant)
- xi Focal or diffuse tissue involvement

Where essential to the diagnosis, specific findings should be discussed (see Section 8.3.3 below):

- i Clinical features
- ii Microscopy (architecture and cytology)
- iii Immunophenotypic findings
- iv Genetic findings
- v Recommendations for further action or investigation (where appropriate)

8.4.2 Reporting of ancillary studies¹⁶

Immunophenotyping

- i State whether flow or histochemistry, FS or PS
- ii Specify all markers investigated, positive or negative
- iii Avoid the use of terms such as ‘T-cell marker’
- iv Specify which cells are positive or negative
- v Specify the percentage of cells and cellular staining pattern where relevant
- vi Discuss diagnostic interpretation and significance
- vii State where performed if reference laboratory used (attach that laboratory’s report)

Molecular or cytogenetic studies

- i Type of specimen used (FS versus PS)
- ii Method (SB, PCR, conventional cytogenetics, FISH, etc.)
- iii Specify test conditions (primers targets, etc.)
- iv Discuss diagnostic interpretation and significance. (This requires an understanding of the test performance characteristics specific for the laboratory that performs the test — see Chapters 6 and 7)
- v State where performed if a reference laboratory is used and attach that laboratory’s report

8.4.3 Statement of diagnostic certainty

As there are many factors which may detract from the degree of diagnostic confidence; and as the treating clinicians may have to manage patients on the basis of reports from pathologists who are unknown to them, we recommend that all pathological reports of lymphoma include a clear statement of diagnostic confidence level (see Table 8.1 for a suggested synoptic report). This may be simply expressed by stating that a diagnosis is either ‘definitive’ or ‘provisional’. A report incorporating a provisional diagnosis should clearly document the reasons for diagnostic uncertainty, with recommendations for further action to achieve a definitive diagnosis.

8.4.4 Recommendations for further action or investigation given in the report

Recommendations given within a pathology report may include any of the following:

- i Rebiopsy (indicating preferred modality)
- ii Specific investigations (e.g. imaging of specific areas)
- iii Referral of pathology material for a second opinion

8.4.5 Synoptic reporting of lymphoma

Synoptic formats have been widely adopted for pathology reporting in oncology, yet lymphoid neoplasia has proven an exception. This reporting format provides a roadmap for diagnostic testing.

Key point

A synoptic approach to reporting is encouraged wherever possible.

To assist in this, a checklist is provided as Table 8.1. It includes recent recommendations from the Association of Directors of Anatomical Pathology in the United States¹⁶, together with possible values for each heading.

It is noted that integration of information from the full blood examination and bone marrow biopsy (if done) will be desirable as synoptic reporting is developed. However, this will present practical problems as this data may emerge from different laboratories.

Table 8.1 Synoptic reporting of lymphoproliferative disease

Synoptic report template for lymphoproliferative disease

SurnameFirst name Ref. No. Sex ... DOB.....

BIOPSY SITE	
<input type="checkbox"/> Nodal	<input type="checkbox"/> Extranodal <input type="checkbox"/> Unknown
DIAGNOSIS	
<input type="checkbox"/> WHO category (specify)	% Follicular (if appropriate):
	Grade (if appropriate):
	ICDO-3/Snomed /SNOP code:.....
<input type="checkbox"/> Lymphoma, unclassified*	
<input type="checkbox"/> Atypical lymphoid hyperplasia*	
<input type="checkbox"/> Haematolymphoid neoplasm NOS*	
<input type="checkbox"/> Reactive lymphadenopathy (specify).....	
<input type="checkbox"/> Non-lymphoid tumour (specify).....	
Comment:	
Diagnostic certainty:	
<input type="checkbox"/> Definitive diagnosis	
<input type="checkbox"/> Provisional diagnosis only*	

*** For unclassified lymphomas, haematolymphoid neoplasm NOS, atypical lymphoid hyperplasia or provisional diagnosis state:**

Differential diagnosis(es):

Uncertainty due to:

- Insufficient material
 - Morphological artefact
 - Immunophenotype undetermined
 - Immunophenotype ambiguous
 - Genotype undetermined
 - Genotype ambiguous
 - Discordant clinicopathological pattern
- Comment:

Further action recommended or taken:

- None
 - Further immunophenotyping (specify)
 - Further genotyping (specify)
 - Rebiopsy: (specify type - NCB, Excisional, etc.)
 - Further clinical investigations: (specify)
 - Second opinion sought from: (specify)
 - Other:
- Comment:

LINEAGE & CLONALITY

Lineage: Null / B-cell / T-cell / NK/T-cell / Histiocytic / Dendritic / Myeloid / Non-haemopoietic / Not tested / Indeterminate / Other.....

Clonality: Monoclonal / Oligoclonal / Polyclonal / Unknown

Clonality assessed by: Immunohenotype / Genotype / Inferred from morphology

SPECIMEN

Specimen type: **Cytology:**
FNA / Body Cavity Fluid / Other

Tissue biopsy:
NCB (state gauge) / Incisional / Excisional / Resection (state type) / Endoscopic / Bone marrow / Peripheral blood

Specimen dimensions:.... X ... X ... mm

Received: Fresh / In saline / In formalin / Other

Consultation material: Stained slides / Unstained slides / Paraffin blocks / Other

Specimen triage: Paraffin / Flow / Imprints / Microbiology / Frozen / EM / Tissue Bank / Cytogenetics

Checklist of relevant clinicopathological features

CLINICAL

Disease duration:	Unknown (specify).....
Known sites of disease:	<i>Nodal sites: (specify)</i> Unknown / Solitary/Localised / Generalised <i>Extranodal sites:</i> Unknown / Liver / Spleen / Thymus & Ant. Mediastinum / Waldeyer's ring / Skin / Bone / Peripheral blood / Pleura, pericardium, peritoneum / Disseminated
Organomegaly:	Unknown / Hepatomegaly / Splenomegaly / Other (specify)
Constitutional symptoms:	Unknown / Yes / No
Relevant Haematology:	Unknown / Specify:.....
Relevant clinical Hx:	Unknown / Autoimmune Disease / Medication (eg phenytoin)
Immunosuppression:	Unknown / Viral / Congenital / Transplantation / Methotrexate / Other
Provisional clinical Dx:	Unknown / NHL / Hodgkin lymphoma / Reactive / Other (Specify)...
Previous lymphoma:	Unknown / No / Yes Prev. Diagnosis:..... Date: Site: Stage: Treatment(s): Treatment: Ongoing / Completed (date.....) Response: CR / PR

MORPHOLOGICAL

Degree of involvement:	Partial / Complete
Architectural pattern:	Indeterminate / Diffuse / Mantle zone / Sinusoidal / Follicular / Marginal zone / Paracortical / Pseudofollicular / Nodular / Composite / Other
Tumour cell size:	Indeterminate / Small / Intermediate / Large / Mixed small/large / Other
Cellular features:	Indeterminate / Monomorphous / Polymorphous / Granulomatous / Histiocyte rich / T-cell rich / Eosinophil rich / Neutrophil rich / Sarcomatoid / Other
Cytomorphology:	Indeterminate / Pleomorphic / Hyperlobate / Cerebriform / RS-like / Prolymphocytic / Centroblastic / Paraimmunoblastic / Immunoblastic / Anaplastic / Plasmacytic / Plasmablastic / Monocytoid / Centrocyte-like / Clear cell / Giant cell / Signet ring cell / Other.....
Secondary features:	None / Necrosis / Sclerosis / Angiocentricity / Erythrophagocytic / Epidermotropic / Lymphoepithelial lesions / Enteropathic / Amyloid / Other
Interpretation of results:
Correlation with diagnosis:	Typical / Atypical or variant / Discordant / Non-contributory

IMMUNOPHENOTYPING

Flow studies:	Positive: Negative:.....
Immunohistochemistry:	Positive: Negative:.....
Interpretation of results:
Correlation with diagnosis:	Typical / Atypical or variant / Discordant / Non-contributory

CYTOGENETICS:

Results & Interpretation:	Not done / Conventional / FISH / Other (specify)
Correlation with diagnosis: Typical / Atypical or variant / Discordant / Non-contributory

GENOTYPING

PCR	Not done / Done
	F/S / P/S
IgH	+ve / -ve
TCR	+ve / -ve
t(14;18)	+ve / -ve
Other (specify)
Southern blot:	Not done / Done
Results & interpretation:
Correlation with diagnosis:	Typical / Atypical or variant / Discordant / Non-contributory

8.5 References

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