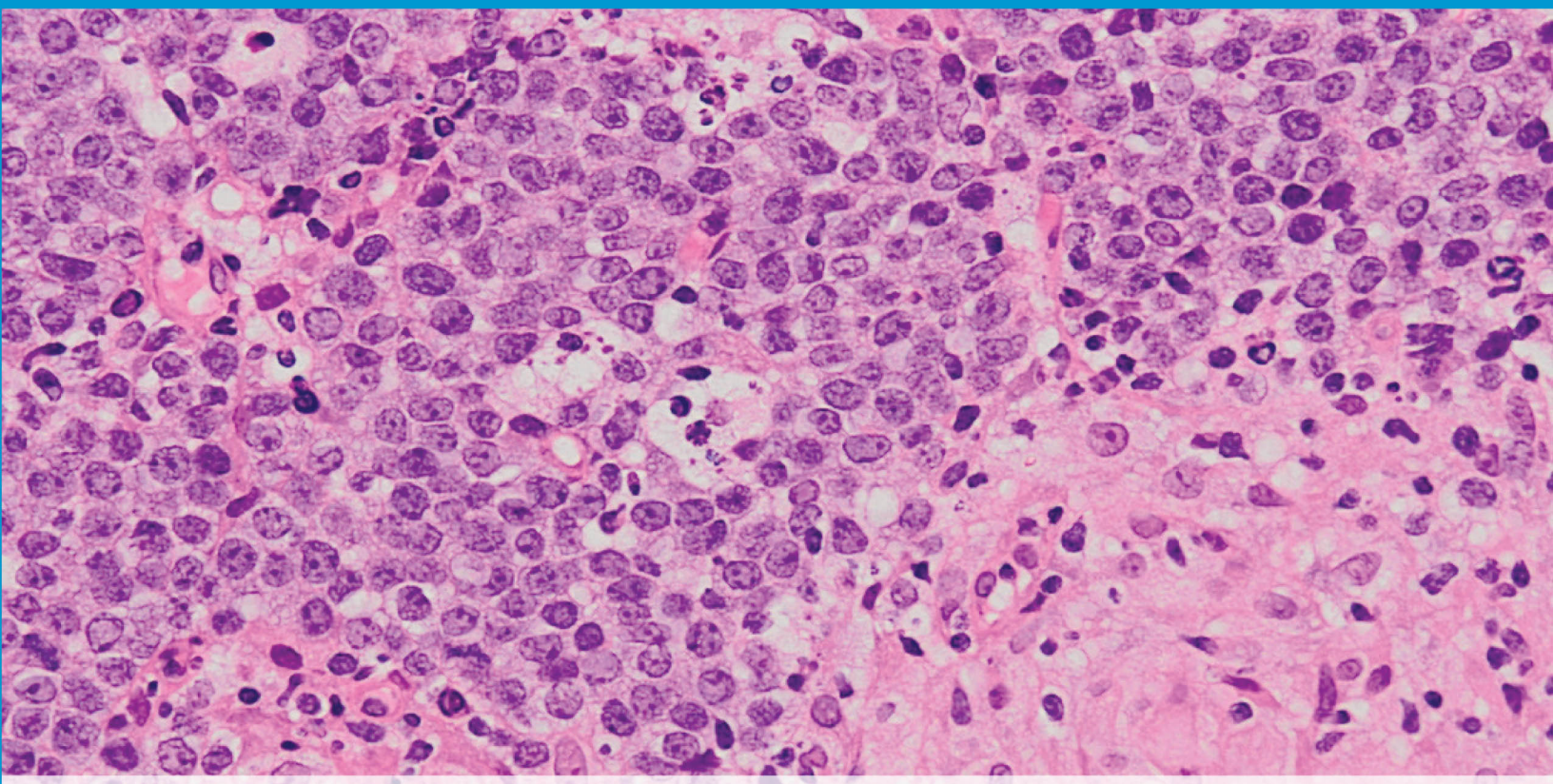
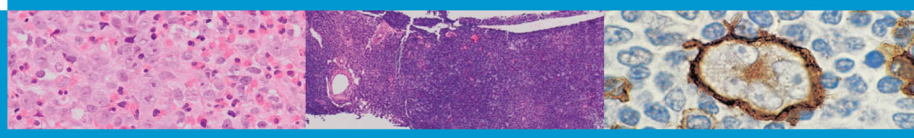


# Diagnostic Lymph Node Pathology

## THIRD EDITION



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THIRD EDITION

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## THIRD EDITION

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# Contents

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# Preface to the third edition

When our new publishers invited us to update *Diagnostic Lymph Node Pathology* with a third edition we were happy to comply. This has enabled us to include a few new items, to improve some of the illustrations and to introduce new ones. The text and references have been updated. We have retained the chapter on the handling of lymph node biopsies and revised the chapter on needle biopsies. The format of the book remains as before with the use of high-quality illustrations and boxes to succinctly present the clinical, morphological, immunohistochemical and genetic features of each entity. The text is concise and is accompanied by relevant and up-to-date references. These features make the book more than an atlas. Our aim has been to create a readily available guide to the correct diagnosis and categorisation of lymph node pathology.

It is the custom in many administrations to refer biopsies diagnosed as malignant lymphoma to a panel of expert haematopathologists for confirmation of the diagnosis. Our hope is that this book will help general pathologists to identify cases in need of referral and to provide a readily available source of information as a bench book for trainees, for general pathologists and also for haematopathologists.

This book was originally conceived by Professor Anthony Leong. Sadly, Professor Leong died at the time the second edition of the book was published.

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# Preface to the second edition

Although it is only four years since this book was first published, our understanding of the biology and pathology of malignant lymphomas, and consequently the way we interpret lymph node biopsies, has changed to the point where a new edition has become necessary. An additional stimulus has been the publication of a new edition of the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, in which a number of new entities are recognized, and some regrouping has taken place.

Our main aims remain the same: to provide general histopathologists and trainees with a systematic and logical way of approaching lymph node biopsies; to help them use diagnostic techniques wisely, in particular the bewildering variety of antibodies now available for immunohistochemistry; and to guide them through the maze of differential diagnoses, enabling them to reach an accurate diagnosis. If specialized haematopathologists are tempted to keep a copy hidden in a desk drawer for quick reference we would be more than gratified. We recognize the important role molecular techniques now play in providing supporting evidence, but, as before, the emphasis throughout is on morphology, supplemented by immunohistochemistry.

It is easy to become excited by new entities and concepts. While including these, we hope we have managed to preserve the balance of the text, without giving undue prominence to rarities. At the same time, we have attempted to provide a reasonably complete guide to lymph node pathology, so that the answer to most diagnostic problems will be found in these pages. We should emphasize that this is not a comprehensive guide to malignant haematopathology: only those conditions that involve lymph nodes, either primarily or secondarily, are discussed. This inevitably means that some important conditions, for example some forms of extranodal T-cell lymphoma, are either not considered or receive only brief mention.

The general format of the book has been retained and the layout has, we think, been improved. For quick reference, the boxes containing concise clinical, morphological and immunohistochemical features of each entity have been preserved and updated. A number of illustrations have been replaced and additional ones included. The layout of the illustrations has been changed to avoid boxes that overflow onto two pages, a major criticism of the previous edition. The references given are by no means comprehensive. We have included those that we regard as being seminal, useful reviews or evidence of recent significant advances, and we hope the interested reader will find these a useful starting point.

Since the previous edition the use of needle core biopsies has increased substantially. In expert hands, they provide a rapid and increasingly reliable means of diagnosis, with minimal inconvenience and discomfort for the patient. Chapter 11 has been expanded to reflect this and to provide a guide to their interpretation and limitations.

We hope our efforts have resulted in a useful and practical guide to a subject that remains endlessly challenging and fascinating.

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# Preface to the first edition

Haematopathology has become the subject of specialist reporting in many countries in the developed world. This is seen as a necessary evolution and a consequence of the increasing complexity of the subject, the need for sophisticated ancillary investigations in some cases and the fundamental need for an accurate diagnosis on which to base further patient management. Nevertheless, most lymph node biopsies will land on the desks of general pathologists who will need to make the judgement as to whether the pathology is that of a reactive or neoplastic process and whether referral is necessary. We have aimed this book at general pathologists and trainees, although we hope that dedicated haematopathologists may find some gems between its covers. In light of our target readership we have placed our main emphasis on morphology rather than molecular techniques.

A number of authors have tried to base lymph node diagnosis on the low power structure of the node. While this is a good starting point it is not always helpful and can be misleading. For example, although an overall nodular pattern is characteristic of follicular lymphoma it can also be the dominant low-power feature of mantle cell and marginal zone lymphomas. We would nevertheless emphasize the importance of both low-power and high-power morphological examination based on good-quality sections. It is wise to arrive at a diagnosis, or differential diagnosis, based on morphology before ordering or embarking on the interpretation of immunohistochemical preparations. In the final analysis the morphology and immunohistochemistry should be compatible, and it is the concordance of these techniques that provides security of diagnosis.

We are aware of the time constraints facing pathologists and have aimed to make the basic information on entities easily accessible by presenting the clinical, morphological and immunohistochemical features of each disease together with illustrations in boxes. More detailed information is provided in the text.

Since we began writing this book we have seen a year-on-year growth of the proportion of lymph node biopsies received as needle biopsies. These are usually taken by radiologists using CT guidance. The most obvious value of this technique is in taking biopsies of deep-seated lesions and thus avoiding the need for surgery. Most pathologists would probably wish that superficial nodes were obtained by whole lymph node biopsy. However, as clinicians realize that a definitive diagnosis can be obtained on a high proportion of superficial nodes using needle biopsies, this type of biopsy is likely to become more common in view of its ease of application and low morbidity. We have therefore included in the book a chapter specifically on the interpretation of needle biopsies.

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# Acknowledgements

Firstly, we would like to thank Dr Bruce Addis and the previous editors for their work on the first two editions, without which there would not be a third edition. We thank our friends and colleagues in the South West Region for a constant supply of biopsy material. We are particularly indebted to Dr Denis Madders (Royal Bournemouth and Christchurch Hospitals) and Dr Kudair Hussein (Poole Hospital NHS Trust) for their help in the provision of illustrative cases. Dr Hilary Lawton (Peterborough Hospital) provided sections and photographs of unusual cases, and Professor John Chan (City of Hope, Duarte, California) provided material for the illustrations of Kimura disease, for which we are most grateful.

Dr Fabio Facchetti (Spedali Civili-University of Brescia) was most generous in the provision of Figures 3.40–3.42. Professor Ethel Cesarman (Weill Cornell Medical College) most generously provided the illustrations in Figure 8.11. We would like especially to express our warm gratitude to colleagues at Southampton General Hospital (Dr Vipul Fiora and Dr Sanjay Jogai) for their unremitting support in the identification and retrieval of representative cases. Finally, we wish to thank Barbara Norwitz and Henry Spilberg of CRC Press for their help and guidance.

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# Abbreviations

**AITL** angioimmunoblastic T-cell lymphoma

**ALCL** anaplastic large cell lymphoma

**ALK** anaplastic lymphoma kinase

**ALL** acute lymphoblastic leukaemia

**ALPS** autoimmune lymphoproliferative syndrome

**AML** acute myeloid leukaemia

**ANKL** aggressive NK-cell leukaemia

**ATLL** adult T-cell leukaemia/lymphoma

**B-CLL/SLL** chronic lymphocytic leukaemia/small lymphocytic lymphoma

**B-PLL** B-cell prolymphocytic leukaemia

**BSAP** B-cell lineage activator protein

**cHL** classical Hodgkin lymphoma

**CVID** common variable immunodeficiency

**DLBCL** diffuse large B-cell lymphoma

**EATL** enteropathy-associated T-cell lymphoma

**EBER** Epstein–Barr virus–encoded RNA

**EBNA** Epstein-Barr nuclear antigen

**EBUS** endobronchial ultrasound

**EBV** Epstein–Barr virus

**EMA** epithelial membrane antigen

**ESR** erythrocyte sedimentation rate

**EUS** endoscopic ultrasound

**FDC** follicular dendritic cell

**FISH** fluorescence in-situ hybridization

**FL** follicular lymphoma

**FNA** fine needle aspiration

**GCET1** germinal centre B cell expressed transcript-1

**HCL** hairy cell leukaemia

**HCv** hairy cell variant

**H&E** haematoxylin and eosin

**HGAL** human germinal centre-associated lymphoma gene

**HHV-8** human herpesvirus 8

**HIV** human immunodeficiency virus

**HMFGP** human milk fat globule membrane

**H/RS** Hodgkin/Reed–Sternberg

**HTLV** human T-cell lymphotropic virus

**HVCD** hyaline vascular Castleman disease

**ICOS** inducible T-cell co-stimulator

**IDRC** interdigitating reticulum cell

**Ig** immunoglobulin

**IgA** immunoglobulin A

**IgD** immunoglobulin D

**IgG** immunoglobulin G

**IgH** immunoglobulin heavy chain

**IgM** immunoglobulin M

**IRTA1** immunoglobulin superfamily receptor translocation-associated 1

**ISH** in-situ hybridisation

**LBCL** large B-cell lymphoma

**LBL** lymphoblastic lymphoma

**LCA** leukocyte common antigen

**LDCHL** lymphocyte depleted classical Hodgkin lymphoma

**LDH** lactate dehydrogenase

**LEF1** lymphoid enhancer-binding factor-1

**LGL** large granular lymphocyte

**L&H** lymphocytic and histiocytic

**LMP1** latent membrane protein

**LPL** lymphoplasmacytic lymphoma

**LRCHL** lymphocyte rich classical Hodgkin lymphoma

**LYG** lymphomatoid granulomatosis

**MALT** mucosa-associated lymphoid tissue

**MCCHL** mixed cellularity classical Hodgkin lymphoma

**MCD** multicentric Castleman disease

**MCL** mantle cell lymphoma

**MUM1** multiple myeloma oncogene

**MZL** marginal zone lymphoma

**NK** natural killer

**NLPHL** nodular lymphocyte-predominant Hodgkin lymphoma

**NOS** not otherwise specified

**NSCHL** nodular sclerosis classical Hodgkin lymphoma

**PAS** periodic acid-Schiff

**PCD** plasma cell variant Castleman disease

**PCR** polymerase chain reaction

**PDC** plasmacytoid dendritic cell

**PEL** primary effusion lymphoma

**PLL** prolymphocytic leukaemia

**PMBL** primary mediastinal (thymic) large B-cell lymphoma

**PNET** primitive neuroectodermal tumour

**PTCL** peripheral T-cell lymphoma

**PTGC** progressive transformation of germinal centres

**PTLD** post-transplant lymphoproliferative disorder

**SCID** severe combined immunodeficiency

**SLE** systemic lupus erythematosus

**TCR** T-cell receptor

**TdT** terminal deoxynucleotidyl transferase

**TFH** T-follicular helper

**THRLBCL** T-cell/histiocyte–rich B-cell lymphoma

**TIA-1** T-cell intracellular antigen 1

**T-PLL** T-cell prolymphocytic leukaemia

**WHO** World Health Organization

**XLP** X-linked lymphoproliferative disorder

**ZAP-70** zeta chain–associated protein kinase 70

# 1

# Handling of lymph node biopsies, diagnostic procedures and recognition of lymph node patterns



## TAKING AND HANDLING OF LYMPH NODE BIOPSIES

Suboptimal techniques in the taking and handling of lymph node biopsies are probably the biggest obstacle to achieving a correct diagnosis. All concerned with this process should bear in mind that the objective of the biopsy is to achieve a timely and accurate diagnosis on which the subsequent management of the patient can be based. Feedback information at multidisciplinary team meetings is a valuable means of achieving and maintaining a high diagnostic standard of lymph node biopsies. In the absence of such meetings, personal contact is needed to ensure that any shortcomings in the biopsy technique and handling of the specimen are rectified.

Lymph nodes should be selected for biopsy on the likelihood that they contain the pathological process. They should be dissected out whole, if possible, and with the capsule intact. Fragmented nodes may be more difficult to diagnose than intact nodes, depending on the pathological process involved. Traction artefacts are usually most severe when the biopsy tissue is very fibrotic or has to be taken from a confined space, such as the anterior mediastinum.

Needle biopsies are now more frequently used for the diagnosis of lymph node pathology. When possible, open lymph node biopsies should be used for superficial, accessible lymph nodes; however, needle biopsies have a lower morbidity than open biopsies and are of particular value in sampling mediastinal, abdominal and retroperitoneal lymph nodes, avoiding the need for more invasive procedures, such as laparotomy. These biopsies are usually taken by radiologists using ultrasound or computed tomography (CT) guidance. If fixed quickly, needle biopsies give good morphological preservation, which, together with immunohistochemistry, allows the precise identification of most common lymphomas. The technique may be less successful in the identification of non-neoplastic proliferations. The handling and preparation of needle biopsies is discussed in more detail in Chapter 11.

Fine needle aspiration (FNA) biopsies have their greatest value in the separation of carcinoma from lymphoma and for the identification of recurrences or for staging. The role of this technique for the primary diagnosis of lymphoma is limited and presents many pitfalls unless in the hands of an expert cytopathologist. Alternatively, the lymph node aspirates obtained via ultrasound-guided endoscopic (endoscopic ultrasound [EUS]) or endobronchial (endobronchial ultrasound [EBUS]) sampling may be processed entirely as clot preparations, without making aspirate smears, thereby maximising the material available for immunohistochemistry. Additional information may be obtained if a separate aspirate sample is sent for flow cytometry. Ideally, the clot preparations obtained will contain lymph node microbiopsies, and serial sections may be stained with haematoxylin and eosin (H&E) whilst the intervening spare sections may be used for immunostaining or other special stains (Figure 1.1).


Figure 1.1 Series of sections from a fine needle aspiration cell block preparation demonstrating the use of 'spare sections' between haematoxylin and eosin (H&E) levels for immunohistochemistry.

Logistics dictate that many laboratories receive their lymph node biopsies in fixative. In such cases, the volume of the fixative should be at least ten times that of the specimen. Whole lymph nodes should be sliced as soon as possible to allow rapid penetration of the fixative.

Ideally, lymph node biopsies should be received fresh in the laboratory immediately after excision. This requires good communication between the pathologist and surgeon or radiologist, to ensure that there is minimum delay in the specimen reaching the laboratory. A slice taken from one end of the node can be gently touched onto a clean glass slide, and air-dried and stained by one of the rapid Romanowsky techniques to provide a rapid cytological assessment. Pathologists experienced with this technique may be able to give a provisional cytological diagnosis from this when appropriate. The technique is most useful, however, in determining the subsequent handling of the specimen in the laboratory. The slice of lymph node used to make the imprint preparation may be frozen for subsequent molecular investigation. It should not be used for histology, if this can be avoided, since the process of making imprint preparations often causes traction artefacts in the tissue (Box 1.1).

Fresh tissue may be sent for cytogenetic analysis and/or flow cytometry in appropriate cases. Frozen sections may be cut for morphology and immunohistochemistry when indicated. One or more slices of the node should be placed in fixative overnight or longer for histology and immunohistochemistry. Needle biopsies require a similar period of fixation. Fortunately, for diagnostic purposes a wide range of procedures, including immunohistochemistry, polymerase chain reaction (PCR) and fluorescence *in-situ* hybridization (FISH), can be performed on fixed tissue (Box 1.2).

## PROCESSING, SECTIONING AND STAINING

Laboratories should maintain quality control of their reagents and equipment to ensure adequate processing, cutting, staining and immunohistochemistry. Cell morphology is important in haematopathology and can easily be obscured or distorted by poor fixation, processing and sectioning. Section thickness has a marked influence on cytological and histological appearances. The optimum thickness is 3–5 µm.

H&E is the stain most widely used in histopathology and is often the only one used in lymph node diagnosis. The Giemsa stain can add another dimension to haematopathology and is the stain of choice for this subspeciality in much of mainland Europe. The Giemsa stain highlights basophilia and eosinophilia, and this aids the identification of blast cells, plasma cells, eosinophils and mast cells.

### BOX 1.1: Fresh whole lymph node biopsies

Slice using clean sharp blade; use slices as follows:

- Imprint cytology (tissue used to make imprints should not be used for histology) may be used for:
  - Rapid evaluation
  - Air-dried imprint slides stored for fluorescence *in-situ* hybridization (FISH) if required
- Histology and immunohistochemistry. Place slices in fixative; if using formalin fix for 12–24 hours
- Fresh tissue slices may be used for:
  - Cytogenetics
  - Molecular analysis
  - Cell culture
  - Microbiology

### BOX 1.2: Fixed whole lymph node biopsies

- Cut into 5-mm slices with a sharp scalpel as soon as possible after biopsy
- Place in fixative, at least ten times the volume of the specimen
- Leave in fixative for 12–24 hours if formalin is the fixative
- Tissue for long-term storage should be blocked in paraffin after fixation, not left in fixative