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Editors

Atlas of Cutaneous Lymphomas

Classification and Differential Diagnosis

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To my parents, who instilled in me their love of teaching and caring for others. To my daughters, Seija, Annika, and Kaia for bringing a joyous perspective to each day. And finally to my husband, Pete, who helps keep our lives in balance and our family on course.

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To my parents, Nita and Nakul Goyal; grandparents, Krishan and Pushpa Raheja; aunt, Nina Raheja; siblings, Kavita and Nihkil Goyal; cousin, Meera Jain; and last, but not least, my best friend, Daniel O'Leary. This book would not have been possible without your love, encouragement, and support.

Amrita Goyal, M.D.

To my father, Robert McDivitt, the best pathologist I know and my first teacher. To my mother, who taught me the power of small steps to reach a goal. To Micki, Elias, Allie, and Sam, no longer children, they continue to bring joy and teach me about life. And finally to my husband, Frank, who inspires me to enjoy.

Lyn McDivitt Duncan, M.D.

Preface

This atlas was inspired by the Massachusetts General Hospital Cutaneous Lymphoma Conference, a multidisciplinary meeting of dermatologists, dermatopathologists, hematopathologists, medical oncologists, and radiation oncologists. We have found that the integration of clinical findings, laboratory results, and disease progression is critical for the diagnosis and treatment of patients with skin lymphoma. Using the clinical and histological images of our patients as the framework, this atlas follows the recent classification scheme for cutaneous lymphoma published by the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group.

Our intent was to produce an atlas of clinical and histological images with diagrams, tables, and text describing each entity in the current cutaneous lymphoma classification scheme. The outline of each chapter includes an introduction with synonyms, clinical features (presentation, prognosis, and treatment), laboratory findings (histopathology, immunophenotype, and molecular), differential diagnosis, and presentation of clinical cases. In addition to chapters for each diagnostic entity, we have included introduction chapters for T-cell lymphomas, B-cell lymphomas, a chapter on ancillary techniques including immunohistochemistry and molecular tests, and a glossary of terms.

We hope this resource will help clarify the conceptual framework underlying the classification of cutaneous lymphoma. More importantly, we hope to have produced a book that will serve as a helpful reference for physicians involved in the diagnosis and treatment of patients with cutaneous lymphoma.

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We acknowledge the invaluable contributions of our patients who share their stories and allow us to further understand the diversity of these diseases. This work is also inspired by the teachings of our mentors, Dr. Nancy Harris, Dr. Tom Kupper, and Dr. Martin Mihm; they have taught us many lessons including the value of shared knowledge.

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Introduction and a Brief History of Cutaneous Lymphoma Classification

1

Amrita Goyal, Joi B. Carter, Nancy Lee Harris, and Lyn McDivitt Duncan

Over the past decade, a worldwide consortium of dermatologists, oncologists, hematopathologists, and dermatopathologists has collaborated to develop a unified classification scheme for lymphomas, including primary cutaneous lymphomas. Every year, new publications and workshops lead to a clearer understanding of the nuances of diagnosis and treatment of cutaneous lymphomas. Over the past 20 years, advances in the classification of cutaneous lymphomas have revolutionized the clinical and histopathologic approaches to diagnosis and treatment of these highly varied diseases. This chapter outlines some aims of this book and offers a brief history of cutaneous lymphoma classification.

1.1 Goals of This Book

Understanding cutaneous lymphoma can be challenging for even the most determined, for several reasons:

1. Some of these diseases share clinical presentations.
2. Some display similar histopathological features.
3. While immunophenotypic and genetic features may support a specific diagnosis, there is overlap between tumors.
4. The terminology used to describe these tumors has evolved and only in the past decade has there been a more uniform approach to classification.
5. Few textbooks offer concise descriptions of the clinical and histopathologic characteristics of these diseases in accordance with the most recent classification system. This atlas seeks to fill that gap.

This book was written with several goals in mind:

1. Assemble an atlas of cutaneous lymphomas, organized according to the most recent classification system, as designed by the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC)
2. Offer flowcharts and other schemas to help organize the cutaneous lymphomas in an easy to understand format
3. Provide a concise summary of current knowledge about the clinical presentation, histopathological, immunophenotypic and genetic characteristics, prognosis, and treatment of each cutaneous lymphoma
4. Demonstrate the importance of clinical–pathologic correlation using real clinical cases, in most cases by juxtaposing both the clinical and histopathologic images from the same patients
5. Present this information at a level appropriate for students, trainees, and practitioners in dermatology and pathology.

1.2 History of the Classification of Cutaneous Lymphomas

For more than a century and a half, lymphomas arising in the skin were classified as one of three entities: mycosis fungoides, Sézary syndrome, or spread of lymphoma from a noncutaneous site. Although mycosis fungoides was first described

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by Alibert [1] in 1806, and Sézary syndrome in 1938 [2], it was not until the 1970s that primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome were differentiated from cutaneous manifestations of systemic lymphoma. At that time a classification system reflecting the heterogeneity of cutaneous lymphomas began to be developed.

At the end of the last century, it became increasingly clear that a wide range of B-cell and T-cell lymphomas can occur as primary tumors in the skin, and that they have quite variable clinical outcomes: some primary cutaneous lymphomas are indolent and never disseminate to extracutaneous sites, while others disseminate widely with an aggressive clinical course. This variability in clinical outcome is one of the primary reasons that an accurate classification system is necessary.

From the 1970s to the 1990s, there were three principal classification schemes for lymphomas: Kiel [3–5], Lukes-Collins and Working Formulation [6], all based predominantly upon morphological findings and cell type [7]. In many cases diagnoses were reported using more than one scheme's terminology. However, in 1994, the International Lymphoma Study Group achieved an international consensus on the classification of lymphomas. This led to the publication of the Revised European–American Lymphoma Classification (REAL) [8]. The REAL classification incorporated morphologic, immunologic, genetic, and clinical features to identify "real" biological entities. The REAL Classification also recognized the differences between nodal and extranodal lymphomas. Shortly thereafter, the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Program Project Group devised a classification scheme specifically for primary cutaneous lymphoma [9]. In addition to the features used in the REAL classification scheme, the EORTC scheme incorporated the clinical presentation and biologic behavior of the lymphomas.

In 2001, the World Health Organization (WHO) International Agency for Research and Cancer published *The Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, 3rd edition [10]. Although EORTC schema for understanding the cutaneous T-cell lymphomas was largely integrated into this WHO publication, there continued to be debate about the subtypes of cutaneous B-cell lymphomas and their relationships to their nodal counterparts. Points of contention included: the use of terms "primary cutaneous" versus "extranodal," "diffuse follicular lymphoma" versus "diffuse large B-cell lymphoma," "follicle centre" versus "follicular," and the use of "leg type" in describing primary cutaneous B-cell lymphoma not arising on the leg. In 2003 and 2004, the authors of the WHO and EORTC classifications met in Lyon and Zurich to resolve these issues through review of cases and active discussion. This review included not only the histopathological, immunophenotypic, and genetic features of the tumors, but their clinical outcomes and response to therapy. These meetings resulted in the 2005 joint EORTC/WHO classification for primary cutaneous lymphoma [11].

In 2008, the 4th edition of the *WHO Classification of Tumours of Haematopoetic and Lymphoid Tissues* was published. This volume, "the blue book," integrated the primary cutaneous lymphoma classification into the broader classification of nodal and other extranodal lymphoma classification [12]. The integrated EORTC and WHO classification has become the basis for diagnosis and treatment of patients with cutaneous lymphomas. Persistent inconsistencies between the WHO/EORTC (2005) and WHO (2008) classifications include the use of the terms, primary cutaneous marginal zone lymphoma and CD4+ CD56+ hematodermic neoplasm, in the former and the terms extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and blastic plasmacytoid dendritic cell neoplasm in the latter. Because the WHO classification found in the "blue book" encompasses all leukemias and lymphomas, it can be cumbersome and challenging for dermatologists and dermatopathologists to dissect out the information on skin-specific diseases. Our aim is to provide a resource for diagnosis of primary cutaneous lymphomas that includes clinical and histopathological images of the diseases described in accordance with the most recent classification scheme. We refer to the classification as WHO-EORTC to recognize the important contributions of both of these groups.

1.3 Terminology

The field of cutaneous lymphomas is rife with terminological ambiguity. For example, the term "primary cutaneous" is itself controversial. It has been used by some to describe lymphoma arising in the skin without evidence of concurrent extra-cutaneous lymphoma after staging (often including both radiological and bone marrow evaluation) [9, 13]. While no longer used, early on some defined primary cutaneous lymphoma as lymphoma arising in the skin without evidence of extra-cutaneous lymphoma *for 6 months* following initial presentation [14]. In the WHO-EORTC Classification, the term "primary cutaneous lymphoma" refers to cutaneous lymphomas that present in the skin without evidence of extracutaneous disease at the time of diagnosis [11].

The majority of lymphomas are named descriptively after their cell of origin. For example, "primary cutaneous follicle centre lymphoma (pcFCL)" is a tumor composed of neoplastic BCL-6+ follicle center B cells. This biologically based, descriptive naming system carries two complications. First, names of the lymphomas are changed as new biological information is discovered. For example, what was once CD4+ CD56+ hematodermic neoplasm is now called blastic plasmacytoid dendritic cell neoplasm, because of better

understanding of the cell of origin of the disease. A better understanding of the risk of progression has led some disease entities to be divided and re-defined; for example the Ketron-Goodman variant of pagetoid reticulosis is now considered to be best classified as either aggressive epidermotropic CD8+ cutaneous T-cell lymphoma or cutaneous gamma-delta T-cell lymphoma, depending on the immunophenotype. Second, given the descriptive terminology, the names of these diseases can be up to seven to eight words long, as with primary cutaneous CD4+ small-medium pleomorphic T-cell lymphoma. One student even suggested that cutaneous lymphoma may be the one case in which eponymous naming might actually make things *easier*. There has even been discord over these extensive descriptive names. For example, while some prefer "extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)," others use the term "primary cutaneous marginal zone lymphoma (pcMZL)." The use of the term "extranodal" indicates that this tumor is biologically related to those occurring at other extranodal sites (most commonly the gastrointestinal tract); however, some argue that the use of "MALT" is inappropriate given that the skin is not mucosa.

Other terms require understanding of the specific classification criteria, for example subcutaneous panniculitis-like T-cell lymphoma (SPTCL). This lymphoma is defined as a tumor of cytotoxic T cells with an alpha-beta TCR. Although lymphomas with a gamma-delta TCR phenotype were once grouped with SPTCL and may occur predominantly in the subcutaneous fat, given evolving information about their clinical progression, these lymphoma are now classified separately as primary cutaneous gamma-delta T-cell lymphoma.

One of the aims of this book is to help clarify some of this confusion. We list synonyms at the beginning of every chapter and note shifts in terminology based on medical advances. In each chapter we have used tables and illustrations to help organize the approach to diagnosis of primary cutaneous lymphoma. Finally, we have included a glossary of terms to provide a quick reference to access the occasionally cryptic terminology.

1.4 Case-Based Approach in Primary Cutaneous Lymphomas

The diagnosis of primary cutaneous lymphomas requires the correlation of clinical and laboratory findings. At the Massachusetts General Hospital, a dedicated team of experts in Dermatology, Hematology-Oncology, Hematopathology, Dermatopathology, and Radiation Oncology diagnose and treat patients with cutaneous lymphoma. This group meets regularly to review the clinical, histopathological, immunophenotypic, and genetic features of patients with a comprehensive evaluation of the ongoing evolution of patients' disease including recurrence, dissemination, and response to therapy. As a patient's disease evolves, his or her clinical picture is revisited, underscoring the importance of clinical pathological correlation over time.

The cases presented in this atlas are derived from this experience: nearly all the cases represent patients who were diagnosed and treated at the Massachusetts General Hospital. Most chapters contain examples of complete cases of patients with primary cutaneous lymphoma including images of both clinical and histopathological findings. Juxtaposition of clinical and pathologic images from a single patient helps enhance an understanding of clinical and pathological correlations. Overall, we hope that this work is a practical tool for those who care for patients with cutaneous lymphoma.

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Introduction to Cutaneous Lymphomas

2

Amrita Goyal, Joi B. Carter, and Lyn McDivitt Duncan

The term *cutaneous lymphoma* encompasses an array of neoplasms that vary widely in their clinical presentation, prognosis, histopathology, immunohistochemistry, and molecular biology. The World Health Organization–European Organization for Research and Treatment of Cancer (WHO/EORTC) classification system recognizes 15 primary cutaneous lymphomas (Table 2.1). These lymphomas are divided into three overarching categories: T-cell lymphomas, B-cell lymphomas, and precursor neoplasms. Each chapter in this book is dedicated to one of these cutaneous lymphomas and offers a clinical and histopathologic description, differential diagnosis, and one or more clinical cases. Our intent in writing this book is to familiarize the reader with the most recent classifications of the cutaneous lymphomas, offer relevant clinical and histopathologic characteristics, and provide direction in navigating the often difficult task of distinguishing the various forms of cutaneous lymphoma.

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Table 2.1 WHO-EORTC classification of cutaneous lymphomas

Lymphoma	Abbreviation	Incidence (%)
T-cell lymphomas:	CTCL	77
Mycosis fungoides	MF	50
Sézary syndrome	SS	3
Adult T-cell leukemia/lymphoma	ATLL	<1
Subcutaneous panniculitis-like T-cell lymphoma	SPTCL	1
Extranodal NK/T-cell lymphoma	eNK/TCL	<1
CD30+ lymphoproliferative disorders:	CD30+ LPD	
Primary cutaneous anaplastic large cell lymphoma	pcALCL	8
Lymphomatoid papulosis	LyP	12
Provisional entities:		
CD8+ aggressive epidermotropic T-cell lymphoma	CD8+ AECTCL	<1
Primary cutaneous gamma-delta T-cell lymphoma	pcGDTCL	<1
CD4+ primary cutaneous small-medium pleomorphic T-cell lymphoma	pcSMPTCL	<1
B-cell lymphomas:	CBCL	23
Primary cutaneous marginal zone lymphoma	pcMZL	7
Primary cutaneous follicle center lymphoma	pcFCL	11
Primary cutaneous diffuse large B-cell lymphoma, leg-type	pcDLBCL	4
Intravascular large B-cell lymphoma	ivLBCL	<1
Precursor neoplasms:		
Blastic plasmacytoid dendritic cell neoplasm	BPDCN	<1

Adapted from Willemze et al. [1] and Swerdlow et al. [2]
The abbreviations used throughout this book and the incidence of each lymphoma are listed

2.1 The Skin as an Immune Organ

The skin is one of the most important organs of the immune system and plays a critical role in both the innate and adaptive immune systems. There are a variety of immune cells present in the skin, including T cells, B cells, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils, mast cells, monocytes, and macrophages [3]. It is possible for any of these cell populations to become deranged and develop into a neoplasm (Fig. 2.1) [5].

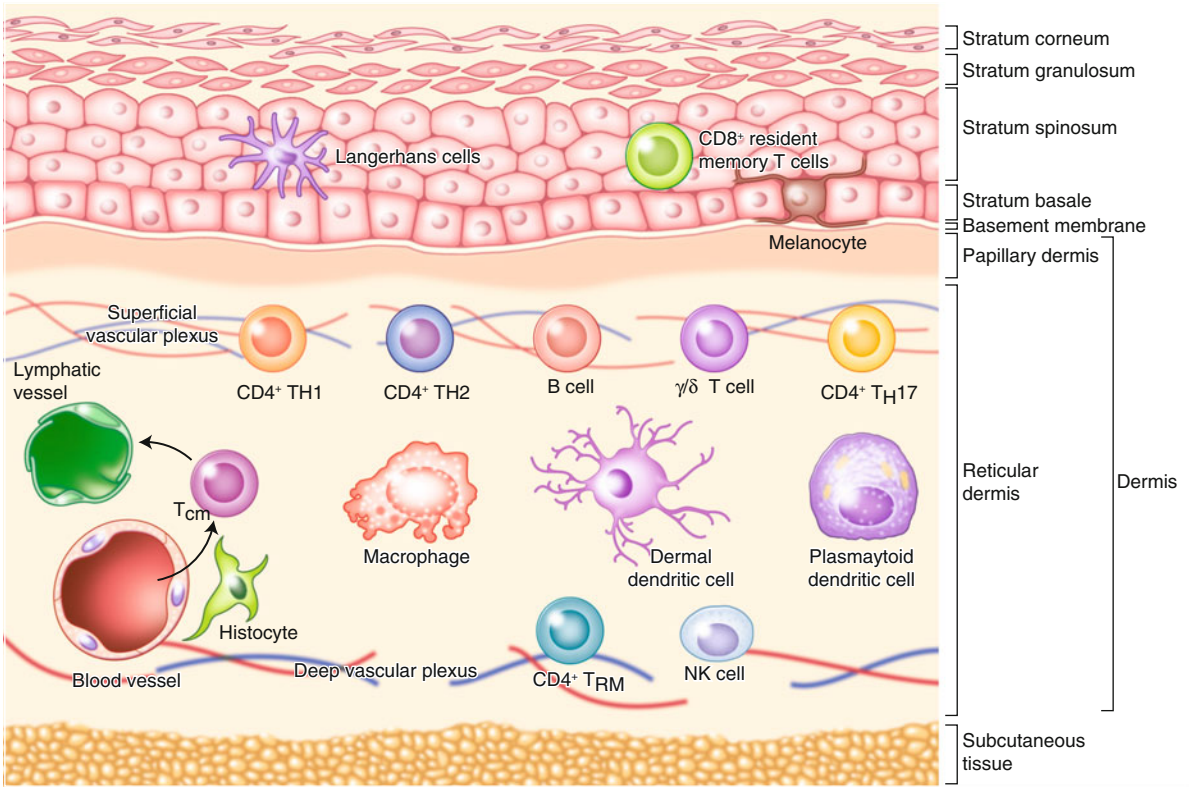

Fig. 2.1 The skin is one of the most important organs in the immune system. The epidermis is usually inhabited by CD8+ T cells and Langerhans cells. A number of cell types reside in the dermis, including CD4+ T cells of various phenotypes (including TH1, TH2, and TH17 cells), gamma/delta T cells, B cells, NK cells, mast cells, and plasmacytoid dendritic cells. Circulating memory T cells spend some time in the skin, entering via blood vessels and returning to the circulation via the lymphatics. Note the structure of the skin—the epidermis is composed of four major layers: the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. Melanocytes produce melanin and are intercalated between keratinocytes of the basal layer of the epidermis. The dermis is composed of the looser papillary and underlying denser reticular dermis. The subcutaneous fat lies beneath the dermis (Diagram adapted from Nestle et al. [4])

2.2 Classification of Cutaneous Lymphomas

Cutaneous lymphomas can be segregated into three categories: T-cell lymphomas, B-cell lymphomas, and precursor cell neoplasms. The 15 lymphomas included in the current WHO/EORTC classification schema are listed in Table 2.1 (Fig. 2.2). One schema for organizing these lymphomas is provided in the flow chart in Fig. 2.2.

The lymphomas can be further subdivided based on immunohistochemical phenotypes, as described in the flow chart in Fig. 2.3.

It is important to note that although the majority of these cutaneous lymphomas are *primary cutaneous* lymphomas clinically arising in the skin, several of these neoplasms, including Sézary syndrome, adult T-cell leukemia/lymphoma (ATLL), and intravascular large B-cell lymphoma (ivLBCL), are systemic lymphoid neoplasms. They are included in the classification of cutaneous lymphomas because of their prominent cutaneous findings.

There are many other primary cutaneous lymphomas not included in the WHO/EORTC classification system, some because they are exceedingly uncommon and some because they are not yet well defined.

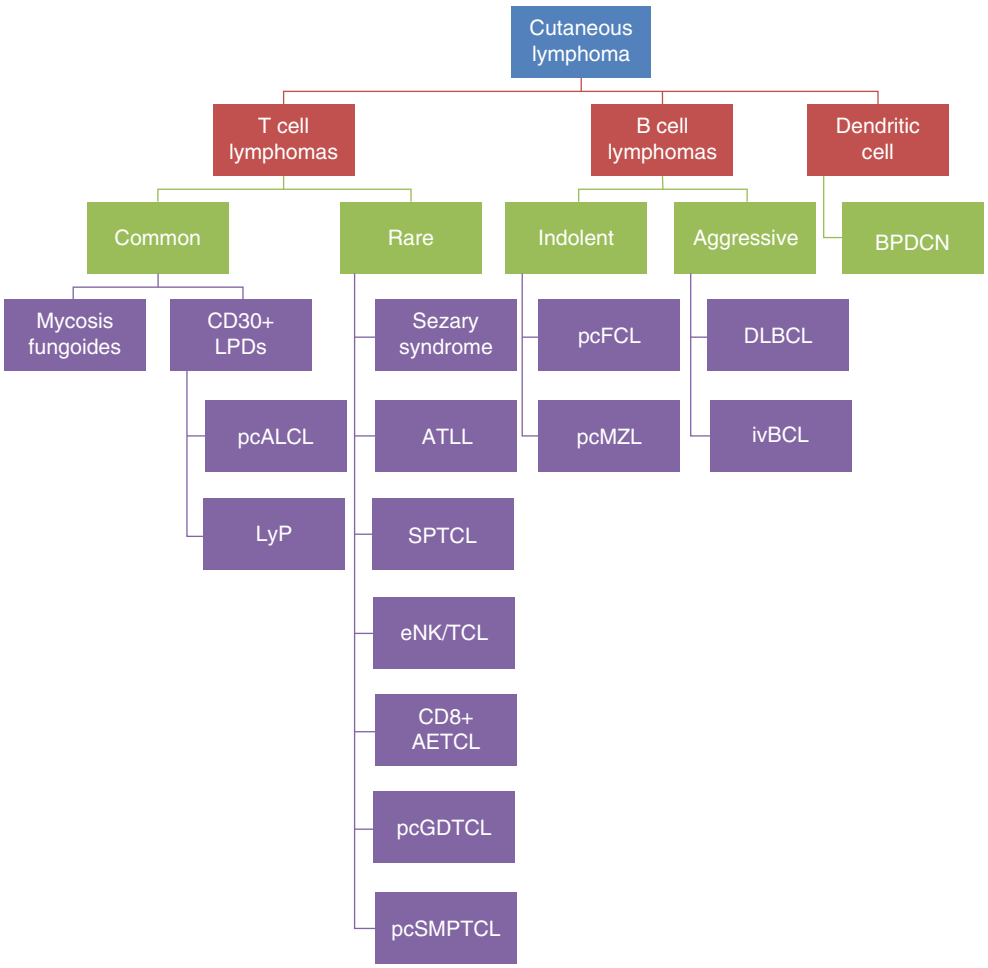

Fig. 2.2 Conceptual framework for cutaneous lymphomas. Cutaneous lymphomas can be broken down in any number of ways, but most commonly they are divided into T-cell neoplasms, B-cell neoplasms, and dendritic cell neoplasms; beyond that classification variations abound. Here, T-cell neoplasms are divided based on frequency—common versus rare. The most common lymphomas are mycosis fungoides (MF) and the CD30+ lymphoproliferative diseases (CD30+ LPDs). The rare T-cell lymphomas are a diverse group, and each one makes up less than 3 % of cases of cutaneous T-cell lymphomas. It is possible to divide the B-cell lymphomas based on prognosis, either indolent or aggressive. Finally, blastic plasmacytoid dendritic cell neoplasm (BPCDN) is the only dendritic cell neoplasm that bears lymphoid markers. *ATLL* adult T-cell leukemia/lymphoma, *DLBCL* diffuse large B-cell lymphoma, leg type, *CD8+ AECTCL* CD8+ aggressive epidermotropic cutaneous T-cell lymphoma, *eNK/TCL* extranodal NK/T-cell lymphoma, *LyP* lymphomatoid papulosis, *ivLBVL* intravascular large B-cell lymphoma, *pcALCL* primary cutaneous anaplastic large cell lymphoma, *pcFCL* primary cutaneous follicle center lymphoma, *pcGDTCL* primary cutaneous gamma/delta T-cell lymphoma, *pcMZL* primary cutaneous marginal zone lymphoma, *pcSMPTCL* primary cutaneous small-medium pleomorphic T-cell lymphoma, *SPTCL* subcutaneous panniculitis-like T-cell lymphoma

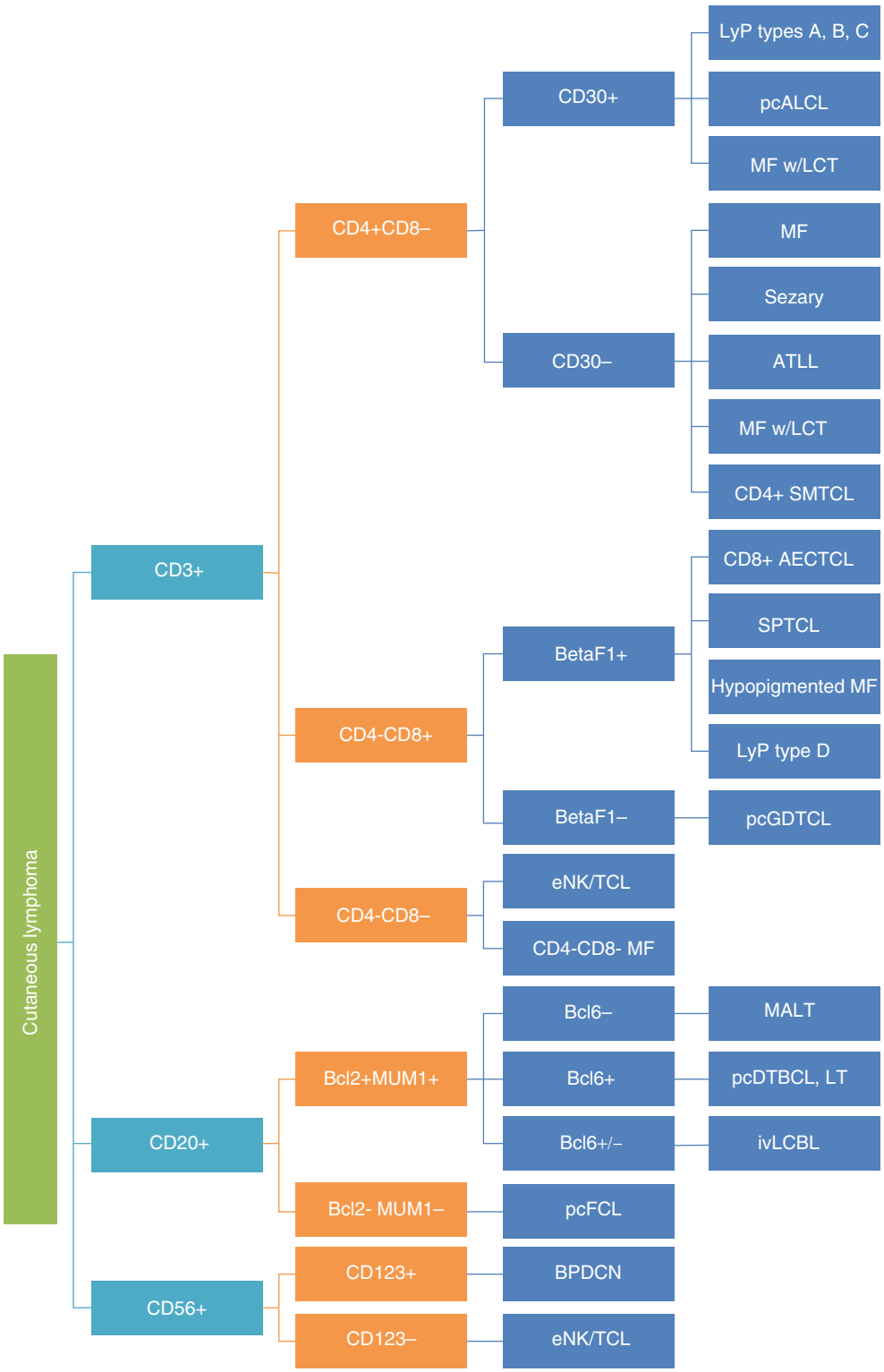

Fig. 2.3 Immunohistochemical flow chart of cutaneous lymphomas. Cutaneous lymphomas can be segregated by cell of origin (T cell, B cell, NK/T cell) or by dendritic cell. CD3+ T cells can be further subdivided based on immunohistochemical markers, including CD4, CD8, and CD30. B-cell lymphomas all stain positively for CD20; useful immunohistochemical stains for further evaluation include Bcl2, Bcl6, and MUM1. While this flow chart describes the archetypical staining patterns for each lymphoma, individual cases may vary. *ATLL* adult T-cell leukemia/lymphoma, *CD8+ AECTCL* CD8+ aggressive epidermotropic cutaneous T-cell lymphoma, *DLBCL* diffuse large B-cell lymphoma, leg type, *eNK/TCL* extranodal NK/T-cell lymphoma, *ivLBVL* intravascular large B-cell lymphoma, *LCT* large cell transformation, *LyP* lymphomatoid papulosis, *MF* mycosis fungoides, *pcALCL* primary cutaneous anaplastic large cell lymphoma, *pcFCL* primary cutaneous follicle center lymphoma, *pcGDTCL* primary cutaneous gamma/delta T-cell lymphoma, *pcMZL* primary cutaneous marginal zone lymphoma, *pcSMPTCL* primary cutaneous small-medium pleomorphic T-cell lymphoma, *SPTCL* subcutaneous panniculitis-like T-cell lymphoma, *SS* Sézary syndrome