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The Landscape of Cutaneous Lymphomas in 2016, An Introduction

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The approach to the classification of cutaneous lymphomas has been challenged by the competing demands of an “organ-specific” approach vs. a desire to better understand common features of lymphomas affecting multiple anatomic sites^{1,2}. For example, some lymphoma subtypes that may present in the skin as well as other anatomic sites, such as extranodal marginal zone lymphoma, share some histological and immunophenotypic features, but still differ in underlying biology and clinical behavior. Conversely, some lymphomas presenting primarily in the skin, such as adult T-cell leukemia/lymphoma or intravascular large B-cell lymphoma may represent manifestations of systemic disease. Particularly for cutaneous lymphomas, knowledge of clinical features is essential to arriving at a specific diagnosis. As an example, lymphomatoid papulosis, transformed mycosis fungoides (MF) and cutaneous anaplastic large cell lymphoma may share some morphological and immunophenotypic features, such that accurate diagnosis is only possible with knowledge of the full clinical picture.

Advances in genomic, proteomic and transcriptome profiling in the last decade have led to the development of additional diagnostic tools and a better understanding of underlying biology, as well as some common recurrent themes shared by systemic and cutaneous lymphomas. Some examples of such included the discovery of *DUSP22* rearrangements in cutaneous anaplastic large cell lymphoma³ and specific subtypes of lymphomatoid papulosis,⁴ the identification of *MYD88* mutations in cutaneous diffuse large B-cell lymphoma, leg type,^{5,6} and the characterization of complex mutational profiles of MF and Sezary syndrome (SS).^{7–11}

Current criteria permit the recognition of primary cutaneous follicle center lymphoma, even in those cases containing a significant component of large centrocytes and centroblasts. Such cases are readily distinguished from examples of diffuse large B-cell lymphoma, leg type, based on the distinct genomic profile and immunophenotypic features of the latter^{12,13}. Not fully understood is the role that site of presentation plays in the diagnosis of cutaneous lymphomas. For example, some cases of primary cutaneous follicle center lymphoma appear to pursue a more aggressive clinical course when presenting on the lower extremities.¹⁴ It

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remains to be determined if there are underlying biological features to explain this altered clinical behavior.

There are also complex interrelationships between certain primary cutaneous lymphomas that are not fully understood. For example, some patients with mycosis fungoides have concomitant, pre-existent or subsequent CD30+ T-cell lymphoproliferative disorders (CD30+ LPD) (lymphomatoid papulosis and cutaneous anaplastic large cell lymphoma), and the same happens to patients with CD30+ LPD and mycosis fungoides.¹⁵ Since the treatment for MF-LCT, LyP and PC-ALCL is so drastically different, pathologists involved in the diagnosis of these disorders need to be aware that a careful exploration of the clinical presentation is imperative for an adequate diagnostic evaluation. To such extent, perhaps the addition of FISH for *DUSP22* might prove to be of benefit. While many new examples of LyP have emerged (type D, E, DUSP22), none of them carry any diagnostic or therapeutic significance. On the other hand, because some of them have a CD8+ phenotype, and can be associated with angionecrosis or angioinvasion, the differential diagnosis includes certain rare aggressive T-cell lymphomas that require aggressive chemotherapy.

Some entities have been newly described or better defined since the last WHO monograph in 2008.¹⁶ Some of the important newcomers include EBV-positive mucocutaneous ulcer (EBV-MCU),¹⁷ a disease that characteristically presents in mucocutaneous sites, in association with varied causes of immunosuppression. While histologically aggressive, spontaneous resolution can occur in 25% of patients. A discussion on the use of the term “lymphoma” vs. “lymphoproliferative disorder” has also significantly influenced some of the diagnostic categories, reflecting the variable clinical course of many of these lesions. On the T-cell spectrum of lymphoproliferative disorders, the original provisional category of small to medium sized CD4+ T-cell lymphoma has been modified to “*lymphoproliferative disorder*,” reflecting its indolent clinical course. The indolent CD8-positive lymphoid proliferations originally described in 2007, usually affecting the ear or other acral sites, have been incorporated into the revised WHO classification, although the term “Primary cutaneous acral CD8-positive T-cell lymphoma” was adopted, based on the cytological atypia encountered in this entity. Hydroa vacciniforme and hydroa vacciniforme-like lymphoma have been also re-classified as “lymphoproliferative disorders” reflecting the varied clinical course seen in diverse populations. The category of primary cutaneous gamma delta T-cell lymphoma has been retained, although a gamma-delta T-cell phenotype can be seen in other conditions, including some cases of otherwise typical mycosis fungoides. New insights have been shed on the nature of cutaneous marginal zone lymphomas, and some have questioned whether the use of a “lymphoma” diagnosis is needed.¹⁸ More recently, the description of two main subtypes of cutaneous MALT lymphoma: a class switched (IgG, rich T-cell background) and non-class switched (IgM, rich B-cell, higher likelihood of extracutaneous involvement) have been documented reflecting both immunophenotypic and clinical differences between the groups.¹⁹ Additionally, novel instances of EBV-positive marginal zone lymphomas have been described.

In this issue of *Seminars in Diagnostic Pathology*, several experts in the field have been brought together to summarize some of recent developments in cutaneous lymphoma diagnosis. Dr. Lorenzo Cerroni provides a summary of the “past, present and future” of the

field. Dr. Rein Willemze discusses the T-cell lymphomas with a panniculitic presentation, particularly focusing on subcutaneous panniculitis-like T-cell lymphoma and primary cutaneous gamma-delta T-cell lymphoma. Dr. Jakki Hopkins provides a summary of the aggressive type of cutaneous T-cell lymphomas with focus on mycosis fungoides/Sezary syndrome, primary cutaneous aggressive CD8+ T-cell lymphoma, and others. Dr. Steven Swerdlow focuses on cutaneous marginal zone lymphomas. Dr. Werner Kempf provides a seminal discussion on CD30-positive LPD, with emphasis on new subtypes. Dr. Laura Pincus summarizes the B-cell lymphomas of the skin, other than MALT lymphomas. Dr. Kojo Elenitoba-Johnson and Dr. Ryan Wilcox discuss the recent molecular developments described in MF and SS. Dr. Mark R. Wick, on the other hand, has focuses on non-hematopoietic lesions that can potentially mimic skin lymphomas. Finally, we provide an indepth analysis of EBV-related skin lymphomas, and their relationship to similar non-cutaneous disorders.

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