Pathologic Diagnosis of Cutaneous Lymphomas

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KEYWORDS

• Lymphoma • Lymphoproliferative • Cutaneous • Skin • Diagnosis • Clinicopathological correlation • T cell • B cell

KEY POINTS

- Clinicopathologic correlation is an essential element in the diagnostic approach to cutaneous lymphomas.
- Cutaneous lymphomas show overlapping histologic and immunophenotypic features, but can differ significantly in their course and prognosis.
- Monoclonality does not necessarily indicate malignancy. Lack of monoclonality does not exclude the diagnosis of cutaneous lymphoma.

INTRODUCTION

Primary cutaneous lymphomas (CLs) comprise a heterogeneous group of lymphocytic neoplasms with a broad spectrum of clinical, histologic, immunophenotypical, and genetic features (**Box 1**).[1–3] The histopathological examination plays an essential role and is often the starting point in the diagnostic workup of CLs. The classification of CLs follows the current World Health Organization (WHO) classification (4th edition, 2008), which is widely accepted by hematopathologists and dermatopathologists.[3] The WHO classification of the tumors of hematopoietic and lymphoid tissues follows the multiparameter approach by defining lymphomas according to their clinical, histopathological, immunophenotypic, and genetic features as well as the side of primary manifestation, which was originally introduced by the Revised European-American Lymphoma classification (REAL).[4,5]

This aim of this review is to provide an approach based on the growth patterns, cytomorphology, phenotypic, and genetic features for primary CLs and to emphasize the impact of clinicopathological correlation.

Pathologic Approach

Histopathologically, various *growth patterns* can be distinguished. Some are more prevalent in certain forms of CLs, whereas others are found throughout the entire spectrum of CLs. The growth patterns and cytomorphology provide first diagnostic hints. For example, epidermotropic infiltrates of small to medium-sized lymphocytes are most commonly found in cutaneous T-cell lymphomas (CTCLs), whereas dense dermal lymphocytic infiltrates, of variable size and cytomorphology, are commonly present in cutaneous B-cell lymphomas (CBCLs).

For practical reasons, 6 major patterns can be distinguished in CLs: epidermotropic, nodular, diffuse, subcutaneous, angiocentric/angiodestructive, and intravascular. Among each growth pattern, additional histopathological features may

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Box 1
World Health Organization classification for lymphoid neoplasms

MATURE T-CELL AND NK-CELL NEOPLASMS

Mycosis fungoides (MF)

MF variants and subtypes:

Folliculotropic MF

Pagetoid reticulosis

Granulomatous slack skin

Sézary syndrome

Adult T-cell leukemia/lymphoma

Primary cutaneous CD30+ T-cell lymphoproliferative disorders

Primary cutaneous anaplastic large cell lymphoma

Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma

Extranodal NK-/T-cell lymphoma, nasal type

Primary cutaneous peripheral T-cell lymphoma

Rare subtypes:

- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)
- Primary cutaneous γ/δ T-cell lymphoma
- Primary cutaneous CD4+ small/medium T-cell lymphoma (provisional entity)

Primary cutaneous peripheral T-cell lymphoma, unspecified

MATURE B-CELL NEOPLASMS

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

Primary cutaneous follicle center lymphoma

Diffuse large B-cell lymphoma, NOS

Primary cutaneous diffuse large B-cell lymphoma, leg type

Primary cutaneous diffuse large B-cell lymphoma, others

Intravascular large B-cell lymphoma

Note: This list is mainly limited to cutaneous lymphomas in the WHO classification.

Data from Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edition. Lyon (France): IARC Press; 2008.

be identified, such as folliculotropic and syringotropic infiltrates or granulomatous features.

- Epidermotropic infiltrates are most commonly found in CTCLs, particularly in their initial disease stage (eg, mycosis fungoides [MF], patch, and plaque stage), throughout the entire disease evolution like in Sézary syndrome (SS), or in cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (AETCL).
- Nodular and diffuse infiltrates are a hallmark of progressive forms of CTCLs (eg, MF tumor stage; peripheral T-cell lymphoma [PTCL] unspecified) as well as CBCLs.
- The subcutaneous growth pattern is typically found in subcutaneous lymphomas, including the subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with expression of T-cell receptor (TCR) α/β and the subcutaneous form of γ/δ T-cell lymphoma, but may rarely be observed as rare variants in other CTCL and CBCL forms.
- Angiocentric and angiodestructive (ie, angioinvasive) infiltrates are characteristic for aggressive T- and T-/natural killer (NK)-cell lymphomas, such as extranodal T-/NK-cell lymphoma, nasal type, and cutaneous γ/δ T-cell lymphoma. Exceptions to the rule are indolent or low-malignant forms of CD30+ T-cell lymphoproliferations as lymphomatoid