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Cutaneous lymphomas—An update 2019

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Abstract

Primary cutaneous lymphomas (CL) are the second most common form of extranodal lymphomas. Cutaneous T-cell lymphomas represent the majority. They are classified according to the WHO classification 2017 and the updated WHO-EORTC 2018 published in the fourth edition of the WHO classification for Skin Tumors monograph. Primary cutaneous acral CD8+ T-cell lymphoma and EBV-positive mucocutaneous ulcer have been listed as new provisional entities. Moreover, the histological and genetic spectrum of lymphomatoid papulosis has been expanded. Recently, prognostic subtypes were delineated for some entities and subtypes of CL such as folliculotropic mycosis fungoides and marginal zone lymphoma. Since CL show overlapping histological features, clinico-pathological correlation is of outmost importance for the diagnosis. Recent studies revealed new biomarkers and genetic alterations underlying the pathogenesis of CL. Moreover, targeted therapies have widened the treatment options particularly for aggressive lymphomas.

1 INTRODUCTION

The group of primary cutaneous lymphomas (CL) are non-Hodgkin lymphomas, which present in the skin without extracutaneous disease at the time of diagnosis. CL exhibit distinct clinical, histological, immunophenotypic, and genetic features. Moreover, CL differ in prognosis and treatment from systemic lymphomas with similar histological features. To reflect the characteristics of CL, the WHO-EORTC classification for CL was introduced in 2005 and in its updated form published in 2018.[1] The definitions and terminology were incorporated in the revised WHO classification 2017 as well as the fourth edition of the WHO classification of Skin Tumors monograph 2018 (Table 1).[2] This review describes the characteristic features of CL.

Table 1. Spectrum of primary cutaneous lymphomas

Cutaneous T-cell lymphomas
Mycosis fungoides (MF)
MF variants
• Folliculotropic MF
• Granulomatous slack skin
• Pagetoid reticulosis
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30-positive lymphoproliferative disorders
• Lymphomatoid papulosis
• Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, rare subtypes
• Primary cutaneous γ/δ T-cell lymphoma
• Primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma (provisional)
• Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder (provisional)

2 CUTANEOUS T-CELL LYMPHOMAS

In contrast to nodal lymphomas, cutaneous T-cell lymphomas (CTCL) represent the majority of CL accounting for approximately 65% to 75% of all CL.[1]

Mycosis fungoides (MF) is the most common CTCL entity representing nearly 50% of all primary CL.[1] Clinically, MF presents in its classic form with erythematous patches, which may evolve to infiltrated plaques (Figure 1). In a subset of patients, large and often ulcerated tumors develop on preexisting plaques. Whereas the prognosis in the patch and limited plaque stage is favorable (5 and 10-year survival rates >90%), the tumor stage shows an aggressive course with extracutaneous spread and risk for death because of sepsis originating from ulcerated tumors. The histological hallmark of MF is an epidermotropic infiltrate of atypical lymphocytes with lining up of lymphocytes along the junctional zone (Figure 2) and formation of intraepidermal clusters of atypical lymphocytes (so called Pautrier microabscesses or collections). Large-cell transformation usually occurs in later stages of the disease.

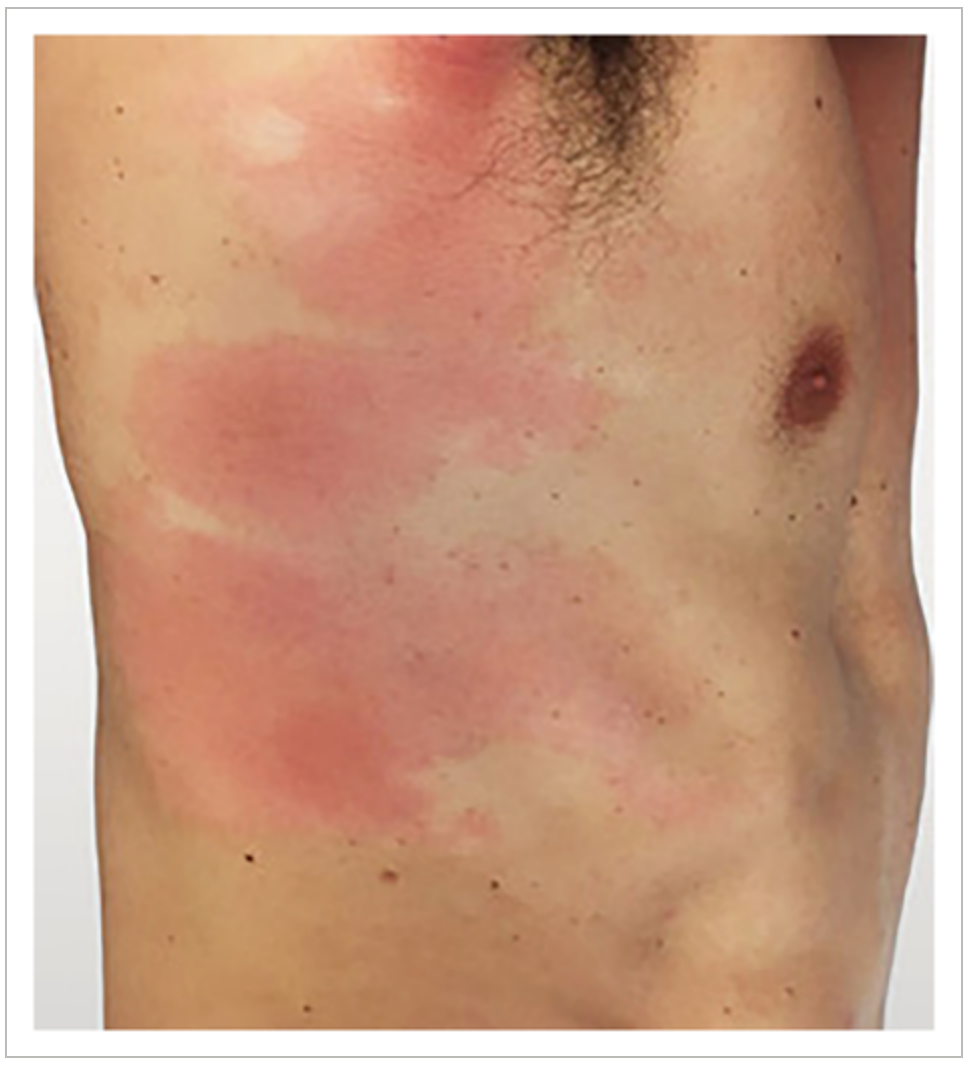

Figure 1

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Mycosis fungoides (patch stage): Erythematous slighty infiltrated lesions (patches) on the trunk

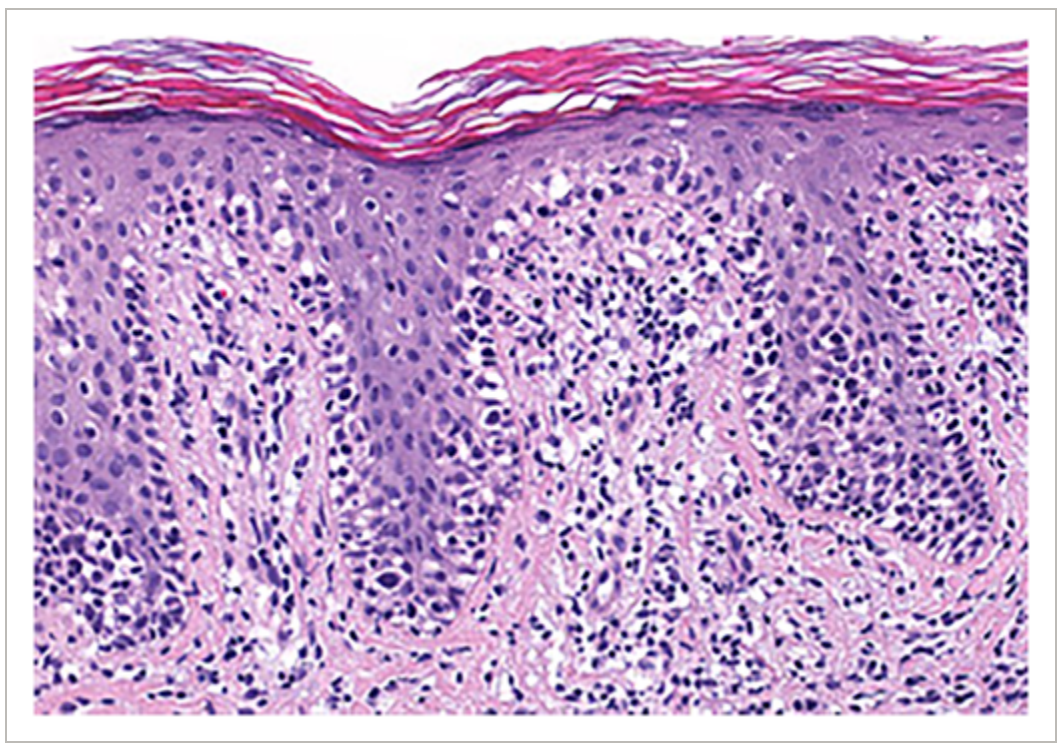

Figure 2

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Mycosis fungoides (patch stage): Epidermotropic infiltrate of atypical small to medium-sized lymphocytes with lining-up of neoplastic cells along the junctional zone

Folliculotropic MF (FMF) is a distinct variant of MF accounting for approximately 10% of all MF cases.[3] It is characterized by predominantly folliculotropic infiltrates (ie, exocytosis of tumor cells into the hair follicle epithelia). The advanced form of FMF with thicker alopecic plaques and deep, dense lymphocytic infiltrates has an aggressive course and needs to be treated more

intensively, whereas the early FMF form with follicular papules, acneiform lesions with comedones and cysts, and alopecic patches run the same indolent course as the classic form of MF.[4] Granulomatous slack skin is regarded as a distinct variant of MF based on its characteristic clinical presentation with development of bulky skin folds, particularly in the intertriginous folds. Pagetoid reticulosis is a variant of MF with an excellent prognosis. It is characterized by a solitary, slowly growing psoriasiform lesion often located on acral sites and histologically by a prominent epidermotropic lymphocytic infiltrate.

Treatment of MF is stage-adapted with skin-directed therapies (UV light, topical corticosteroids, and nitrogen mustard) as the main strategies for early stage of MF and systemic therapies (retinoids, chemotherapy, and targeted therapy) for advanced disease (extensive plaque and tumor stage).[5]

Sézary syndrome (SES) is a rare but aggressive CTCL entity characterized by cutaneous involvement and a leukemic component. Molecular studies showed that the tumor cells in SES are derived from central memory T cells whereas the neoplastic T cells in MF are effector memory T cells.[6] The clinical findings include erythroderma, generalized lymphadenopathy, and an intense pruritus. Atypical lymphocytes with cerebriform nuclei are found in the skin and in the peripheral blood (so called Sézary cells) as well as in the lymph nodes. Based on clinical grounds and because of often unspecific histological findings, distinction of SES from inflammatory skin disorders with erythrodermic presentation such as atopic dermatitis and erythrodermic drug eruptions is challenging. Immunohistochemical markers such as PD-1, TOX, CD7, and the proliferation rate are useful markers in the histopathological diagnosis of SES.[7] Diagnosis requires demonstration of the same clone in the skin lesions and the peripheral blood and one of the following hematologic findings (absolute Sézary cell count of >1000 cells/μL or an expanded CD4+ T-cell population leading to a CD4/CD8 ratio ≥ 10, CD4+/CD7− cells ≥30% or CD4+/CD26− cells ≥40%). Treatment includes extracorporeal photopheresis, alemtuzumab, and chemotherapy.[5]

Primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD) account for approximately 25% of all CTCL thereby representing the second most common group of CTCL. They comprise a spectrum, which includes primary cutaneous anaplastic large cell lymphoma (PC-ALCL), lymphomatoid papulosis (LYP), and borderline lesions.[8] Despite the histological findings are suggestive for a high-grade malignant lymphoma, and recurrences are common, CD30+ LPD run an indolent course and show a good prognosis. PC-ALCL manifests in most cases with a solitary or grouped rapidly growing and often ulcerated large tumor(s). Histology shows dense cohesive infiltrates of predominantly large pleomorphic or anaplastic tumor cells, which express CD30 and a show variable loss of T-cell markers as well as negativity for ALK (p80). Rearrangements of the *DUSP22-IRF4* locus are found in approximately 25% of PC-ALCL. Rearrangements of TP63 are very rare in PC-ALCL. In contrast to systemic ALCL, both chromosomal aberrations seem not to be linked to impaired prognosis in PC-ALCL.

Solitary or grouped PC-ALCL can be treated with surgery or radiation therapy, but relapses are common. Extracutaneous spread and fatal outcome is rare and seems to be more frequent in patients with extensive limb involvement and multifocal PC-ALCL. For those patients, anti-CD30 directed targeted therapy with brentuximab vedotin represents a new and effective treatment option.[9]

Clinically, LYP presents with grouped or disseminated papules and small nodules, which undergo spontaneous regression within few weeks (Figure 3). Five different histological subtypes (referred to as type A-E) and a subtype with chromosomal rearrangements involving the *DUSP-IRF4* locus on 6p25.3 are listed in the current classification.[8] Due to overlapping histological features with other lymphomas, clinico-pathological correlation is crucial for the diagnosis. LYP carries an excellent prognosis. Nevertheless, LYP patients should be followed since they are at risk to develop a second lymphoma, especially MF and Hodgkin lymphoma. In regard to the excellent prognosis, a watch-and-wait strategy for LYP can be justified. Active treatment for LYP includes UV light and low-dose methotrexate, but relapses after withdrawal of treatment are very common.[10]

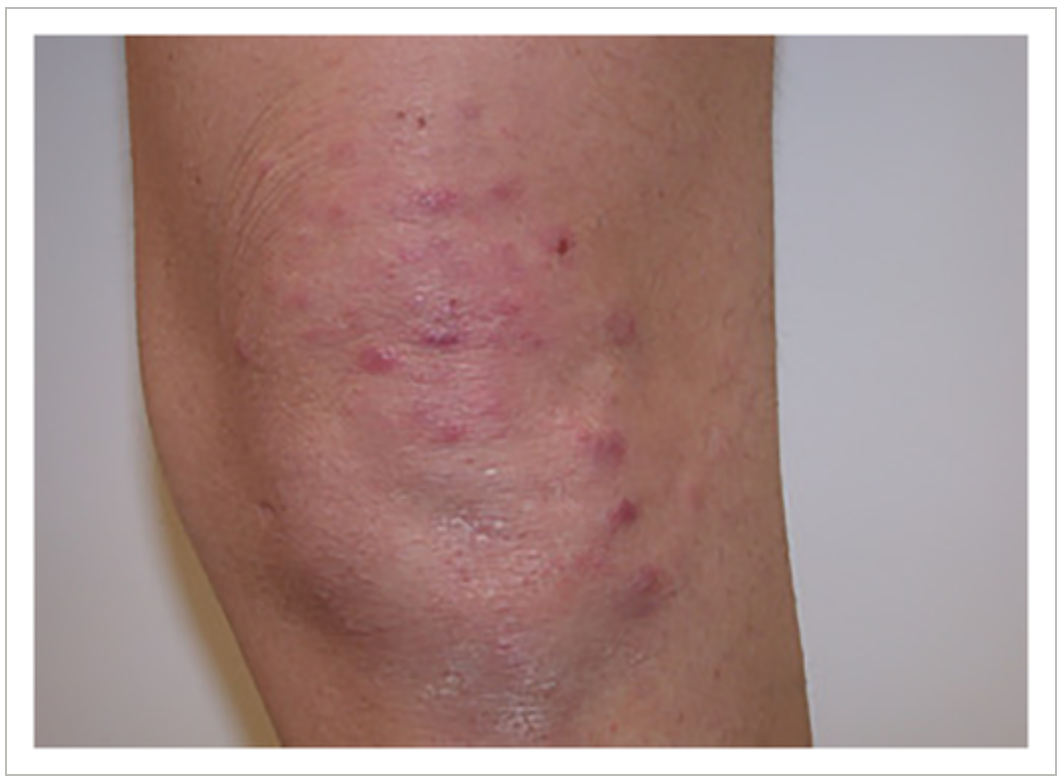

Figure 3

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Primary cutaneous CD30-positive lymphoproliferative disorder; lymphomatoid papulosis: Multiple grouped erythematous to violaceous papules

2.1 Other CTCL forms

CD4+ small/medium-sized T-cell lymphoproliferative disorder (CD4+ SMT-LPD) is still listed as a provisional entity considered as an indolent neoplastic proliferation of follicular T helper cells manifesting with a solitary nodule mostly on the head and neck area.[11] Similar histological and phenotypic features are present in nodular T-cell pseudolymphoma, which cannot be distinguished with certainty from CD4+ SMT-LPD neither clinically nor histologically. For practical reasons, the term CD4+ SMT-LPD may be used to encompass both processes as the prognosis and the treatment are identical, ie, excision or radiation therapy if no regression occurs after incisional biopsy.

Cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8+ AE-CTCL) is very rare but highly aggressive with rapid evolution of necrotic and ulcerated plaques and nodules. Histologically, there is a prominent epidermotropic infiltrate of mostly medium-sized CD8+ (and in 70% of the cases CD45RA positive) lymphocytes and apoptotic keratinocytes.[12] Because of the dismal prognosis, therapy includes multiagent chemotherapy and bone marrow transplantation.

CD8+ acral T-cell lymphoma (CD8+ ATCL) is a provisional CTCL entity, which has newly listed in the revised WHO classification 2017. It presents with a solitary or bilateral nodule(s) at acral sites, ie, ears, face, and feet. Histology shows non-epidermotropic dense dermal infiltrates of small to medium-sized atypical lymphocytes with a characteristic phenotype (CD3+ CD8+ TIA-1+ CD68+).[13] The course is indolent with an excellent prognosis.

Cutaneous peripheral T-cell lymphoma, not otherwise specified (PTL, NOS), refers to CTCL cases which cannot be classified as any of the above-mentioned entities. PTL, NOS cases are heterogeneous in regard to their clinical, histological and phenotypic, and prognostic features. The prognosis is generally bad.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a cytotoxic T-cell lymphoma defined by infiltrates of mostly CD8+ pleomorphic lymphocytes in the lobuli of subcutaneous fat tissue.[14] SPTCL is defined by the expression of TCR alpha/beta by the neoplastic cells, which differs from the expression of TCR gamma/delta by the tumor cells in subcutaneous form of gamma/delta T-cell lymphoma. In most patients with SPTCL, the disease runs an indolent course except for the few patients developing hemophagocytic syndrome linked to an aggressive course with high mortality. Pathogenetically SPTCL carries features of a hyperactive immune reaction, which may explain the fact that immunomodulating therapies are effective in these patients.

Cutaneous gamma/delta T-cell lymphoma (CGD-TCL) is a very rare lymphoma manifesting with rapidly evolving necrotic and ulcerated plaques, nodules, and larger tumors and histologically with epidermotropic and/or dermal and subcutaneous infiltrates.

Other lymphomas such as adult T-cell lymphoma/leukemia, extranodal NK/T-cell lymphoma, nasal type, and chronic active EBV infection are very rare and not discussed in detail in this review.

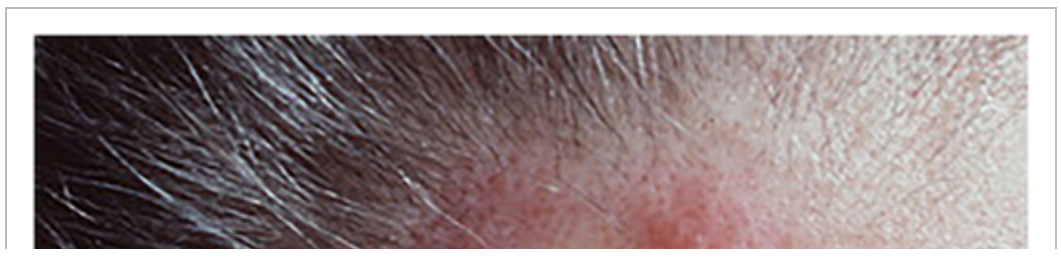
3 CUTANEOUS B-CELL LYMPHOMAS

Cutaneous B-cell lymphomas (CBCL) account for approximately 25% to 35% of all CL. The three most common CBCL entities include primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT).[15, 16] Among rare B-cell proliferations, EBV-positive mucocutaneous ulcer (EBV-MCU) has been included as a new provisional entity in the revised WHO classification 2017.

3.1 Primary cutaneous marginal zone lymphoma

Primary cutaneous marginal zone lymphoma (PCMZL) is an indolent CBCL, which manifests with solitary or multifocal small plaques or nodules mostly on the arms and trunk. Histologically PCMZL consists of small B cells with lymphoplasmacytic or monocytoid morphology, monotypic plasma cells, reactive germinal centers, and numerous T cells. Despite, cutaneous relapses are common (up to 50%). PCMZL exhibits an excellent prognosis (5-year survival rate over 95%-98%).[17] PCMZL shares many histological features with cutaneous B-cell pseudolymphoma and may be induced by similar triggers such as borrelia sp. infection. By some experts, PCMZL is regarded as a clonal chronic cutaneous lymphoproliferative disorder rather than a frank lymphoma.[18] Surgical excision, radiation therapy, intralesional steroids, or intralesional interferon alpha are treatment options.

Primary cutaneous follicle center lymphoma (PCFCL) presents with a solitary or grouped, slowly enlarging nodules mostly on the head and neck area or the upper back (Figure 4). Histologically, a follicular, diffuse, and mixed growth pattern can be distinguished.[16, 19] The tumor cells show a predominantely centrocytic differentiation and express B-cell markers and bcl-6, but are negative for bcl-2 in the vast majority of cases. Surgical excision and/or radiation therapy are the first-line treatment for PCFCL, which runs an indolent course with an excellent prognosis (5-year survival rate over 90%) even if cutaneous relapses occur.



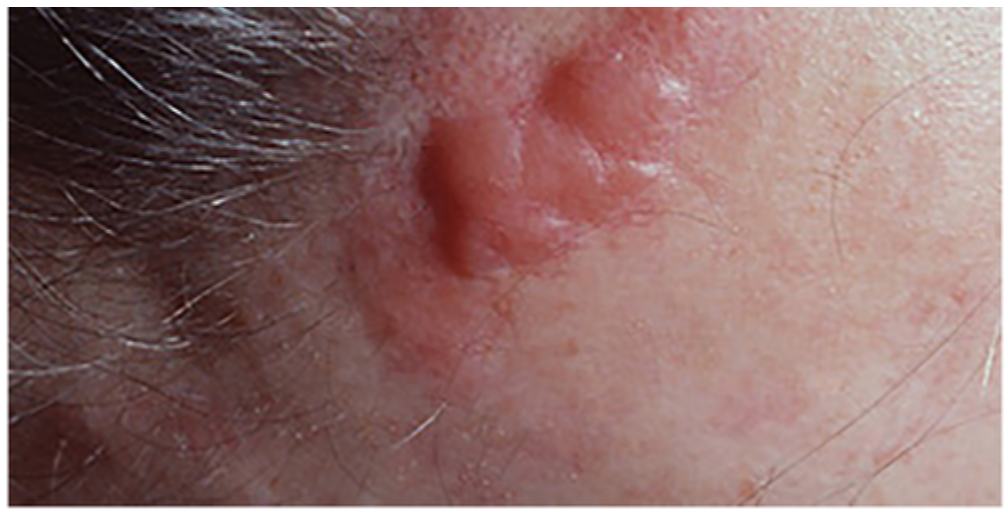


Figure 4

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Primary cutaneous follicle center cell lymphoma: Erythematous nodules with a surrounding plaque on the forehead

3.2 Primary cutaneous DLBCL, leg type

Diffuse large B-cell lymphoma, leg type (DLBCL-LT) is a rare but aggressive CBCL most commonly affecting elderly women and manifesting with rapidly enlarging nodule(s) on one or both legs.[1, 19] More rarely, this lymphoma occurs at other anatomic regions. Histology shows dense infiltrates of mainly centroblastic and/or immunoblastic tumor cells with a distinct phenotype (CD10–, CD20+, MUM-1+, IgM+, bcl-2++, bcl-6 -/+). Spread to extracutaneous organs and death because of lymphoma is not uncommon. Genetic alterations include various translocations (eg, BCL6 and MYC), deletions (eg, BLIMP1; CDKN2A), and mutations (eg, MYD88), which are useful for diagnostic and prognostic purposes.

DLBCL must be distinguished from PCFCL with diffuse growth pattern since these two lymphoma entities significantly differ in regard to their prognosis (20%-60% vs 90% 5-year-survival rate in DLBCL and PCFCL, respectively) and the therapeutic strategy. The distinction is based on the predominant cytomorphology of tumor cells, their immunophenotype, and the clinical context (localization).[16]

EBV-positive mucocutaneous ulcer (EBV-MCU) is a new provisional entity, which is characterized by the development of a rapidly evolving solitary, sharply demarcated ulceration involving the skin, the oropharyngeal mucosa, and gastrointestinal tract in patients with age-related or iatrogenic immunosuppression (eg, methotrexate and ciclosporin A).[20] EBV-MCU is an indolent process, which shows complete remission after withdrawal of underlying immunosuppressive drugs or after radiation therapy.

In summary, CL represent a common form of extranodal NHL with a broad clinical, histological, phenotypic, genetic, and prognostic spectrum. Because of overlapping histological and phenotypic features, clinico-pathologic correlation is crucial for the diagnosis and in consequence also relevant for the therapeutic approach. To enable a better understanding between dermato-oncologist, hemato-oncologist, radiation oncologists, dermato-pathologists, and pathologists, terminology should follow the current classification schemes.

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