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The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas

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Abstract

Primary cutaneous lymphomas are a heterogeneous group of T-cell lymphomas and B-cell lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. In the last decade the 2005 WHO-EORTC consensus classification has served as a golden standard for the diagnosis and classification of these conditions. In September 2018 an updated version of the WHO-EORTC was published in the 4th edition of the WHO classification for Skin Tumours Blue Book. In this classification primary cutaneous acral CD8+ T-cell lymphoma and EBV-positive mucocutaneous ulcer are included as new provisional entities, and a new section on cutaneous forms of chronic active EBV disease has been added. The term primary cutaneous CD4 positive small/medium T-cell lymphoma was modified to primary cutaneous CD4 positive small/medium T-cell Lymphoproliferative disorder, because of its indolent clinical behavior and uncertain malignant potential. Modifications have also been made in the sections on lymphomatoid papulosis increasing the spectrum of histologic and genetic types and primary cutaneous marginal zone lymphomas recognizing two different subtypes.

Herein, the characteristic features of these new and modified entities as well as the results of recent molecular studies with diagnostic, prognostic and/or therapeutic significance for the different types of primary cutaneous lymphomas are reviewed. An update of the frequency and survival of the different types of primary cutaneous lymphomas is provided.

Primary cutaneous lymphomas are defined as non-Hodgkin lymphomas presenting in the skin with no evidence of extracutaneous disease at the time of diagnosis. Primary cutaneous lymphomas include a heterogeneous group of cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL). In the Western world, CTCL constitute approximately 75% -80% of all primary cutaneous lymphomas, and CBCL 20% -25%.[1] These different types of CTCL and CBCL have highly characteristic clinical and histologic features, often a completely different clinical behavior and prognosis compared to morphologically similar nodal lymphomas that may involve the skin secondarily, and require a different type of treatment. Primary cutaneous lymphomas were therefore included as distinct entities in current lymphoma classifications. In the last decade the WHO-EORTC consensus classification has served as a gold standard for the diagnosis and classification of primary cutaneous lymphomas. This classification was published in 2005 and was included in the 2006 WHO classification of Skin Tumours Blue Book.[1;2] Most of that classification was subsequently incorporated in the 2008 WHO classification and its 2016 revision.[3] In August 2018 an updated version of the WHO-EORTC classification was published in the 4th edition of the WHO classification of Skin Tumours Blue Book **(Table 1)**.[4] The terminology and the definitions of the different types of primary cutaneous lymphomas in the updated WHO-EORTC classification are for the most part identical to those used in the 2017 WHO Hematopoietic and Lymphoid Tumour Blue Book. Compared to the 2005 WHO-EORTC classification some new provisional entities have been added, while the terminology of some other conditions has been modified.

In this review the main characteristics of the new and modified disease entities in the updated WHO-EORTC classification are described, and the results of recent molecular studies resulting in new diagnostic and prognostic biomarkers are presented. In addition, an update of the frequency and survival of the different types of primary cutaneous lymphomas, based on data included in the Dutch and Austrian cutaneous lymphoma registries between 2002 and 2017, is provided in Table 2.

Mycosis fungoides, variants of mycosis fungoides and Sézary syndrome

Mycosis fungoides (MF) and Sézary syndrome (SS) are the classic types of CTCL. MF is the most common type and accounts for 60% of CTCL and almost 50% of all primary cutaneous lymphomas.[1] In the WHO-EORTC classification folliculotropic MF (FMF), pagetoid reticulosis, and granulomatous slack skin are recognized as distinct variants of MF, because of their distinctive clinicopathologic features, clinical behavior and/or prognosis. Whereas pagetoid reticulosis and granulomatous slack skin are extremely rare, FMF accounts for approximately 10% of all cases of MF.[5;6] FMF differs from the classic form of MF by the presence of folliculotropic infiltrates, often with sparing of the epidermis, the preferential localization of skin lesions in the head and neck region, and the presence

of (grouped) follicular papules, acneiform lesions, and associated alopecia. Previous studies emphasized that FMF is generally less responsive to several skin-directed therapies and runs a more aggressive clinical course compared to classic MF, and should therefore be treated more aggressively.[5;7;8] However, recent clinicopathologic studies defined a subgroup of FMF patients with an indolent clinical behavior and an excellent prognosis, similar to that of early-stage classic MF.[9;10] Recognition of indolent and more aggressive subgroups of FMF is important from a therapeutic point of view. It suggests that a stepwise, stage-adapted therapeutic approach can be followed, similar as in early and advanced stage classic MF.[11]

Sezary syndrome

Sezary syndrome is a rare leukemic type of CTCL, traditionally defined by the triad of pruritic erythroderma, generalized lymphadenopathy and the presence of clonally related neoplastic T cells with cerebriform nuclei (Sezary cells) in the skin, lymph nodes and peripheral blood. Differentiation between early stage SS and erythrodermic inflammatory dermatoses (EID) may be very difficult.[12] The histologic features of SS may be similar to those in MF. However, the superficial perivascular infiltrates may be sparse, epidermotropism may be minimal or absent, and in as many as one-third of biopsies from patients with otherwise classic SS the histologic picture may be aspecific.[12] Since both clinical and histopathological presentation may be non-specific, demonstration of peripheral blood involvement is crucial for the diagnosis of SS. Criteria for blood involvement include in addition to demonstration of clonally related neoplastic T-cells in skin and peripheral blood, either an absolute Sezary cell count of more than 1000/µL, or an expanded CD4+ T-cell population resulting in a CD4/CD8 ratio ≥ 10, CD4+/CD7- cells ≥ 30% or CD4+/CD26- cells ≥ 40%.

Recent studies described new biomarkers, including among others PD-1 (CD279) and KIRDL2 (CD158k), that can facilitate differentiation between SS and EID both in skin and peripheral blood **(Fig. 1)**.[13;14] Gene expression analyses of circulating Sezary cells showed a characteristic pattern with overexpression of *PLS3*, *TWIST1*, *DNM3*, *EPH4*, *CD158k/KIRDL2* and *NKp46*, and reduced expression of *STAT4*.[15;16] Combinations of these altered genes have been shown to differentiate reliably between SS and EID, but such diagnostic panels are not yet used in daily practice. Genetic alterations in SS are diverse and complex. Recent large-scale genomic studies showed alterations in genes involved in T-cell activation, cell cycle regulation, DNA damage repair, chromatin remodeling, NF-kB activation and JAK-STAT signaling.[17;18] These studies have not only contributed to new insights in the molecular pathogenesis of SS, but also provided new therapeutic targets, which are currently tested in clinical trials (reviewed in [17]).

Primary cutaneous CD30-positive T-cell lymphoproliferative disorders

Primary cutaneous CD30-positive lymphoproliferative disorders (LPD) are the second most common group of CTCL, accounting for approximately 25% of all CTCL.[1] This group includes primary cutaneous anaplastic large lymphoma (C-ALCL) and lymphomatoid papulosis (LyP), which form a spectrum of disease.[1] Because of the overlapping histologic and phenotypic features, clinical presentation and clinical course are used as decisive criteria to differentiate between LyP and C-ALCL and to select the appropriate type of treatment.[19;20] C-ALCL presents as solitary, grouped or, uncommonly, multifocal nodules and tumors. Cutaneous relapses are common, but extracutaneous dissemination occurs in only 10-15% of patients. LyP is characterized by a chronic course of recurrent, self-healing papulononecrotic or nodular skin lesions. The histologic picture of LyP is extremely variable and may resemble different types of CTCL (see Table 2). In addition to the three original subtypes (LyP type A, B and C), the 2018 update of the WHO-EORTC classification also recognizes the more recently described types D (resembling primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma)[21], type E (angiocentric and angiodestructive and clinically characterized by large necrotic eschar-like lesions)[22], a new subtype [23]characterized by the presence of chromosomal rearrangements involving the *DUSP-IRF4* locus on 6p25.3[24] , as well as some even more uncommon variants.[21;22;24] The frequency, predominant phenotype and type of CTCL they mimic are summarized in Table 2. Recognition of these different types of LyP is important to avoid misdiagnosis of other often more aggressive types of CTCL, but has no therapeutic or prognostic implications.

ALK, DUSP22-IRF4 and TP63 rearrangements

In primary systemic ALCL, distinction is made between ALK+ and ALK- ALCL, the former having a much better prognosis. In the group of systemic ALK- ALCL two other recurrent rearrangements have been detected, one involving the DUSP22-IRF4 locus on chromosome 6p25.3, and the other involving the *TP63* gene on chromosome 3q28, which are associated with a favorable and a very poor prognosis, respectively.[25] Unlike systemic ALCL, the vast majority of C-ALCL does not carry translocations involving the *ALK* gene and do not express ALK. Expression of ALK protein therefore strongly suggests secondary cutaneous involvement of a systemic ALK-positive ALCL. However, unusual cases of ALK+ C-ALCL, including both cases showing strong nuclear and cytoplasmic staining characteristic of the t(2;5) chromosomal translocation, and cases expressing cytoplasmic ALK protein, indicative of a variant translocation, have been reported.[26-29] Many of these cases had an excellent prognosis. However, rapid progression to systemic ALCL has been reported as well **(Fig. 2)**. It is at present impossible to predict whether such ALK+ cases presenting with only skin lesions will run an indolent or aggressive course. Rearrangements of the *DUSP22-IRF4* locus are found in approximately 25% of C-ALCL and in a small subset of LyP, but do not have prognostic significance.[30] Histologically,

these lesions show a biphasic growth pattern with CD30+ small cerebriform lymphocytes in the epidermis and large CD30+ transformed cells in the dermis, and show reduced expression of cytotoxic proteins.[24;31;32] *TP63 (*gene) rearrangements are associated with a poor survival in ALK-negative systemic ALCL, but are not or rarely found in C-ALCL.[33;34] A novel recurrent *NPM1-TYK2* gene fusion resulting in constitutive STAT signalling has been described in both C-ALCL and LyP.[35] *TYK2* breaks were found in 15% of primary cutaneous CD30+ LPD. In contrast to tumor stage MF and PTCL, NOS loss of 9p21.3 harboring *CDKN2A* suppressor gene is rarely observed in C-ALCL.[36]

CTCL other than MF, SS and primary cutaneous CD30-positive LPD

CTCL other than MF, SS and primary cutaneous CD30-positive LPD are rare and together account for less than 10% of CTCL.[1] The clinical, histopathologic and immunophenotypic characteristics of these other types of CTCL are summarized in Table 3. Although primary cutaneous gamma/delta-T-cell lymphoma characteristically show a TCRγδ+, βF1- T-cell phenotype, expression of TCRγδ has also been found in rare cases of otherwise classic MF or LyP.[37;38] Such cases have the same indolent course as cases with an αβ T-cell phenotype, and should be diagnosed as MF or LyP, irrespective of phenotype. Conditions that have been modified or have been newly added to the classification, including chronic active EBV infection in childhood, primary cutaneous acral CD8+ T cell lymphoma and primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder**,** are discussed in more detail below.

Chronic active EBV infection in childhood

The updated WHO-EORTC classification contains a new section on EBV-positive lymphoproliferative disorders in childhood, which includes hydroa vacciniforme-like lymphoproliferative disorders (HV-like LPD) and hypersensitivity reactions to mosquito bites (HMB). Both are cutaneous manifestations of chronic active EBV (CAEBV) infection with a risk for progression to systemic EBV-positive T-cell or NK-cell lymphoma.[3 3] In addition, some of these cases will have evidence of systemic CAEBV infection. Most cases of HV-like LPD have a CD8+ T-cell phenotype, while hypersensitivity reactions to mosquito bites more often have a NK-cell phenotype.[39] HV-like LPD is used as an encompassing term for cases previously referred to as HV and HV-like T-cell lymphoma. These disorders are seen mainly in children and adolescents from Asia, or in indigenous populations from Central and South America and Mexico.[40;41]

Clinically, classic HV presents with a papulovesicular eruption on sun-exposed skin areas, in particular the face, the ear lobes and the back of the hands, often with seasonal activity, but without systemic symptoms.[42] In more severe cases skin lesions are localized in sun-exposed and non-exposed skin

areas, facial swelling and extensive ulceration are common, and systemic symptoms, such as fever, wasting, lymphadenopathy, and hepatosplenomegaly may be present.[43;44] Patients with mosquito bite hypersensitivity typically develop ulceronecrotic lesions at the site of the mosquito bite, and may demonstrate similar systemic symptoms as seen in patients with HV-like lymphoma.[40;45]
The clinical course is variable and patients may have recurrent skin lesions for many years before progression to systemic lymphoma

Primary cutaneous acral CD8+ T cell lymphoma

Primary cutaneous acral CD8+ T cell lymphoma is a newly described entity histologically characterized by a diffuse infiltrate of medium-sized CD8+ cytotoxic T cells suggesting an aggressive malignant lymphoma, but with an indolent clinical behavior.[46] This condition, initially designated "indolent CD8-positive lymphoid proliferation of the ear," has been included as a new provisional entity in the updated WHO-EORTC classification.

Patients typically present with a solitary, slowly progressive papule or nodule, preferentially located on the ear or less commonly on other acral sites including the nose and the foot **(Fig, 3A)**.[46;47] These lesions show a diffuse proliferation of clonal medium-sized blast cells throughout the dermis, separated from the epidermis by a clear grenz zone. The atypical cells show a CD3+, CD4-, CD8+, CD30- T-cell phenotype with variable loss of pan-T cell antigens (CD2, CD5, CD7). They are positive for TIA-1, but unlike other types of CD8+ CTCL, negative for other cytotoxic proteins (granzyme B, perforin).[48] CD68 often shows a positive Golgi dot-like staining **(Fig.3)**.[49] In almost all cases, the proliferation rate is very low (<10 percent). Epstein-Barr virus is negative.

The prognosis of this condition is excellent and in typical cases staging is not recommended.[46;47] Skin lesions can easily be treated with surgical excision or radiotherapy. Cutaneous relapses may occur, but dissemination to extracutaneous sites is exceptional.[50] Whether this condition should be labelled lymphoproliferative disorder or lymphoma is a matter of debate, but the majority of the participants at the Clinical Advisory Committee meeting favored the term lymphoma. However, recognition that these lesions have an indolent clinical behavior, despite an aggressive histology, is important to prevent unnecessarily aggressive treatment. Clinicopathologic correlation is essential to differentiate these cases from other types of CD8+ CTCL, such as primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma and cases of CD8+ MF.

Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder

In the 2005 WHO-EORTC classification primary cutaneous CD4-positive small/medium T cell lymphoma was included as a provisional type of CTCL, defined by a predominance of small- to medium-sized CD4+ pleomorphic T-cells without prior or concurrent patches and plaques typical of MF.[1] Patients typically present with a solitary plaque or tumor, generally on the face, the neck, or the upper trunk. Histologically, these lesions show dense, nodular to diffuse dermal infiltrates that mainly consist of CD4+ small-/medium-sized pleomorphic T cells, while a small proportion (<30 percent) of large pleomorphic cells may be present. These cells consistently express the follicular helper T cell markers PD-1(CD279), BCL6, and CXCL13 **(Fig. 4)**.[51;52] The proliferation rate is low, varying between less than 5 percent and at most 20 percent. In almost all cases, there is a considerable admixture with small reactive CD8+ T cells, B cells, and histiocytes including multinucleated giant cells. In some cases monotypic plasma cells may be present.[53] Patients have an excellent prognosis and in typical cases staging is not recommended. If skin lesions do not resolve spontaneously after biopsy, they should be treated primarily with intralesional steroids, surgical excision, or, in rare instances, with radiotherapy.[52]

These cases have the same clinicopathologic and immunophenotypic features and the same clinical presentation and benign clinical course as cases previously referred to as nodular cutaneous pseudo-T-cell lymphomas, and it is highly uncertain if they represent a frank malignancy.[52;54] In the 2016 revision of the WHO classification and in the updated WHO-EORTC classification the term "primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder" rather than lymphoma is therefore preferred.

Rare cases presenting with generalized skin lesions and large, rapidly growing tumors showing on histopathology more than 30 percent large pleomorphic T cells and/or a high proliferative fraction do not belong to this category.[55;56] Such cases usually have a more aggressive clinical behavior and should be classified as peripheral T cell lymphoma, NOS.

Cutaneous B-cell Lymphomas

In the 2005 WHO-EORTC classification three main types of CBCL are recognized: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous large B-cell lymphoma, leg type (PCDLBCL, LT).[1] PCFCL and PCDLBCL, LT were included as separate entities in the 2008 WHO classification for Tumours of Haematopoietic and Lymphoid Tissues and in its 2016 revision.[3] In contrast, PCMZL was not categorized separately, but included in the broad group of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma), notwithstanding differences in histology, genetic profile and clinical behavior.

EBV-positive mucocutaneous ulcer has been included as a new provisional entity in the 2017 revision of the WHO classification and the updated WHO-EORTC classification.

Primary cutaneous marginal zone lymphoma

PCMZL particularly affects young adults and presents with solitary or more commonly multifocal plaques or nodules localized preferentially on the trunk and arms. Cutaneous relapses are common, in particular in patients presenting with multifocal skin lesions, but dissemination to extracutaneous sites is rarely observed. PCMZL have a very indolent clinical course and an excellent prognosis with a 5-year-disease-specific survival rate close to 100%.[57;58]

Recent studies suggest the existence of two types of PCMZL.[59;60] Unlike most other MALT lymphomas, the vast majority of PCMZL express class-switched immunoglobulins including IgG, IgA and IgE, and do not express the chemokine receptor CXCR3, which has been suggested to play a role in the homing of the malignant B-cells to mucosa-associated malignant tissue. These cases show a predominance of T-cells and only a small proportion of neoplastic B-cells. Monotypic plasma cells are usually located at the periphery of the infiltrates and in the superficial dermis beneath the epidermis. Unlike MZL occurring at other sites, these class-switched cases do not show colonization of reactive germinal centers by neoplastic B cells, lymphoepithelial lesions, or transformation into a diffuse large B-cell lymphoma. A small subset of (P)CMZL shows a diffuse proliferation or large nodules of neoplastic B-cells, which express IgM and often CXCR3. These cases share many features with MALT lymphomas at other extranodal sites and are more likely to have extracutaneous disease. The class-switched cases are regarded by some authors as a clonal chronic cutaneous lymphoproliferative disorder rather than an overt lymphoma.[61] This is further supported by clinical and histological similarities between PCMZL and pseudo-B-cell lymphoma (cutaneous lymphoid hyperplasia). The observation that both conditions may develop from chronic stimulation by intradermally applied antigens, such as tattoo pigments, tick bites, antigen injections etc, suggests that they represent a continuous spectrum of cutaneous B-cell proliferations.[62;63]

PCFCL, PCDLBCL, LT and PCDLBCL, other

There has always been much discussion regarding the classification of CBCL with histologic features of a DLBCL. In the 2005 WHO-EORTC classification two types were recognized: PCDLBCL, LT and PCFCL with a diffuse growth pattern. In addition, there was a category PCDLBCL, other.

Differentiation between PCDLBCL, LT and PCFCL is extremely important, since they have a different prognosis and require a different therapeutic approach. PCFCL is a tumor of neoplastic follicle center cells, often with a predominance of large centrocytes, that generally present with localized skin lesions on the head or trunk, can easily be managed by local radiotherapy and have an excellent prognosis. PCDLBCL-LT is a more aggressive type of CBCL, histologically characterized by a monotonous proliferation of centroblasts and/or immunoblasts. These lymphomas particularly affect elderly women and present with generally rapidly growing tumors on one or both (lower) legs, or in approximately 15-20% at sites other than the legs. Compared to PCFCL, they more often disseminate to extracutaneous sites and have a more unfavorable prognosis.[57;64] In addition to clinical and histological criteria, differences in immunophenotype and genetic aberrations may be helpful in distinguishing both conditions (**Table 4)**. In contrast to PCFCL, PCDLBCL, LT strongly express BCL2, IRF4/MUM1 and IgM, and recent studies reported expression of MYC in 65%.[65-68] Since more than 90% of PCDLBCL-LT cases express BCL2, double expression of MYC and BCL2 is also present in two thirds of PCDLBCL-LT cases. Detection of double expression may facilitate differentiation from PCFCL **(Fig. 5)**.[68] Rearrangements of the *MYC* gene have been detected in 30% of PCDLBCL-LT cases, with a second rearrangement in the *BCL6* gene in rare cases.[68]

In the last decade the results of genetic studies have contributed to a better understanding of the molecular mechanisms involved in the pathogenesis of these lymphomas and provided additional diagnostic and prognostic markers. Loss of *CDKN2A* either by gene deletion or promoter methylation and the presence of *MYD88* L265P mutations, both observed in about two-thirds of patients with PCLBCL, LT, have been reported to be associated with an inferior prognosis.[69;70] The presence of *MYD88* L265P mutations and mutations in different components of the B-cell receptor signalling pathway, including *CARD11* (10%), *CD79B* (20%) and *TNFAIP3/A20* (40%) strongly suggest constitutive NF-kB activation in PCLBCL, LT.[71;72] The mutational profile of PCDLBCL, LT, including NF-kB activating mutations and *PDL1/PDL2* translocations, overlaps with that of the ABC-subtype of systemic DLBCL, NOS, but is most similar to that of primary central nervous system lymphomas and primary testicular lymphomas.[73] In contrast to PCDLBCL, LT, *MYD88* L265P mutation is absent and loss or inactivation of *CDKN2A* is not or rarely found in PCFCL. [74;75] PCLBCL, LT should also be distinguished from iatrogenic immunodeficiency–associated lymphoproliferative disorders (see below) and secondary cutaneous DLBCL. In all cases, adequate staging is therefore required.

The term PCDLBCL, other that was introduced in the 2005 WHO-EORTC classification as an encompassing term for rare cases of DLBCL first presenting in the skin, that could not be classified as either PCDLBCL, LT or PCFCL. This term has however been interpreted and used in different ways and

has been the source of much confusion. It has been used for cases composed of large transformed cells that – unlike PCDLBCL-LT – were negative for BCL2, or for cases of PCDLBCL that could not be classified properly using the Hans algorithm.[65;67] However, there are no significant differences between PCDLBCL, LT with or rare cases without expression of BCL2, and categorization of BCL2-negative cases as PCDLBCL, other is therefore not justified.[57;65;76] Moreover, it should be noted that PCDLBCL, LT and PCFCL were already defined on the basis of a combination of clinical, histological, immunophenotypical and genetic criteria long before the Hans algorithm was developed. To avoid further confusion, the 2018 update of the WHO-EORTC classification, like the prior WHO classifications, does not contain a separate category of PCDLBCL, other anymore. In rare cases that cannot be classified as either PCDLBCL, LT or PCFCL, a diagnosis of primary cutaneous DLBCL-NOS should be made.

Intravascular large B-cell lymphoma is a rare disease defined by an accumulation of large neoplastic B-cells within the lumina of blood vessels. These lymphomas typically affect the central nervous system, lungs and skin, and are generally associated with a poor prognosis. A cutaneous variant presenting with skin-limited disease at the time of diagnosis has been described. It accounts for approximately 25% of all cases in the Western world, predominantly affects females, and has a much better prognosis than patients with systemic disease.

EBV-positive mucocutaneous ulcer and other cutaneous immunodeficiency-associated B-cell lymphoproliferative disorders

EBV positive mucocutaneous ulcer (EBVMCU) is defined as a solitary, sharply demarcated ulcerating lesion involving the skin, the oropharyngeal mucosa or gastrointestinal tract in patients with age-related or iatrogenic immunosuppression (methotrexate, azathioprine, cyclosporine, TNF inhibitors). Histologically, the lesions contain large Hodgkin-like EBV-positive B-cells in a mixed inflammatory background. These large transformed cells are PAX5 positive, show variable expression of CD20, display a non-germinal center phenotype (IRF4/MUM1+, CD10-, BCL6-) and typically express CD30 with co-expression of CD15 in almost half of the cases. EBVMCU usually runs a self-limited, indolent course. In iatrogenic cases reduction of immunosuppressive therapy without additional chemotherapy or radiotherapy may result in complete remission.[77]

Apart from EBVMCU, there are other cutaneous manifestations of B-cell LPD occurring in the setting of iatrogenic immunosuppression: skin lesions may be EBV-positive or negative and both can be solitary or generalized with or without ulceration.[78] MTX-associated B-cell LPD usually show the

histology of a DLBCL or Hodgkin-like features.[3] The latter is particularly seen in EBV-positive cases, which account for 40-50% of all cases.[79] Recognition of these iatrogenic immunodeficiency-associated lesions is important, since in all cases reduction or cessation of immunosuppressive treatment may result in (complete) remissions and should be attempted before more aggressive therapy is considered.[78-80]

In conclusion, since the publication of the first WHO-EORTC classification much progress has been made and this 2018 update continues to be a useful guide for clinicians involved in the care for patients with a cutaneous lymphoma. Genome-wide genetic studies have contributed to a better understanding of the molecular pathways involved in the pathogenesis of the different types of cutaneous lymphomas and resulted in the recognition of additional diagnostic and prognostic criteria and new potential therapeutic targets. While genetic markers may become increasingly important, integration of histologic, immunophenotypic, genetic and, in particular in case of cutaneous lymphomas, clinical data remains essential for an accurate diagnosis. In the past decades a multidisciplinary approach with collaboration between pathologists, dermatologists, hematologists and radiation oncologists has been crucial for defining new entities and classifications, and is also the best guarantee for further progress in the diagnosis and treatment of patients with a cutaneous lymphoma.

Authorship

All authors contributed to the contents of this manuscript, which was written by R.W., W.K., E.B, F.F. and E.S.J. and reviewed and edited by all authors.

Conflict-of-interest disclosure

R.W. is member of the Scientific Advisory Board of Takeda. The remaining authors declare no competing financial interests.

Legends to Figures:

Fig. 1. Sezary syndrome. Patient presenting with erythroderma (A); band-like infiltrate of atypical lymphoid cells in superficial dermis with formation of intraepidermal (Pautrier) microabscesses (B); strong expression of CD279 (PD-1) by the neoplastic T-cells is a useful marker to differentiate Sezary syndrome from erythrodermic inflammatory dermatoses (C).

Fig. 2. Cutaneous anaplastic large cell lymphoma presenting with multiple skin lesions on the right lower leg, part of which disappeared spontaneously (A); histologic examination shows a diffuse infiltrate of large anaplastic cells (B), which are positive for CD30 (C) and show cytoplasmic staining for anaplastic lymphoma kinase (ALK) (D). Staging was negative and initially an expectant policy was followed. Twelve months after diagnosis she developed systemic disease with involvement of lungs and bone marrow. Treatment with multiagent chemotherapy was unsuccessful and she died 18 months after diagnosis.

Fig. 3. Primary cutaneous acral CD8+ T-cell lymphoma. (A) Typical clinical presentation with slowly progressive skin tumor on the right ear. (B) diffuse proliferation of medium-sized pleomorphic cells in the dermis; the atypical cells strongly express CD8 (C) and TIA-1 (D). CD68 shows a positive Golgi dot-like staining (E).

Fig. 4. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder. (A) Patient presenting with a tumor on the left cheek. (B) Detail of atypical dermal infiltrate showing a predominance of small/medium lymphoid cells and scattered large lymphoid cells, which express CD4 (C). (D) Expression of CD279/PD-1 by medium-sized to large atypical T-cells, partly arranged in clusters.

Fig. 5. Primary cutaneous diffuse large B-cell lymphoma, leg type. (A) Cohesive sheets of large transformed cells with prominent nucleoli. Strong expression of BCL2 (B), IgM (C) and MYC (D) may facilitate differentiation from PCFCL.

Table 1. Relative frequency and prognosis of primary cutaneous lymphomas included in the 2018 update of the WHO-EORTC classification.

WHO-EORTC Classification 2018	Frequency (%)[#]	5-year DSS (%)[#]
Cutaneous T-cell lymphomas		
Mycosis fungoides	39	88
Mycosis fungoides variants		
• Folliculotropic MF	5	75
• Pagetoid reticulosis	<1	100
• Granulomatous slack skin	<1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30-positive lymphoproliferative disorders		
• Primary cutaneous anaplastic large cell lymphoma	8	95
• Lymphomatoid papulosis	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
• Primary cutaneous γ/δ T-cell lymphoma	<1	11
• Primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma (provisional)	<1	31
• Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
• Primary cutaneous acral CD8+ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, not otherwise specified	2	15
Cutaneous B-cell lymphomas		
Primary cutaneous marginal zone lymphoma	9	99
Primary cutaneous follicle center lymphoma	12	95
Primary cutaneous diffuse large B-cell lymphoma, leg type	4	56
EBV-positive mucocutaneous ulcer (provisional)	<1	100
Intravascular large B-cell lymphoma	<1	72

DSS: disease-specific survival; NDA: no data available;

[#] Based on data included in Dutch and Austrian cutaneous lymphoma registries between 2002 and 2017.

Table 2. Lymphomatoid papulosis: histologic subtypes and differential diagnosis

LyP type	Predominant phenotype	Main differential diagnosis
LyP, type A (>80%)	CD4+, CD8-	C-ALCL Tumor stage MF classic Hodgkin lymphoma
LyP, type B (<5%)	CD4+, CD8-	Plaque stage MF
LyP, type C (10%)	CD4+, CD8-	C-ALCL Transformed MF (CD30+)
LyP, type D (<5%)	CD4-, CD8+	CD8+ aggressive epidermotropic T-cell lymphoma
LyP, type E (<5%)	CD4-, CD8+	Extranodal NK/T-cell lymphoma
LyP with DUSP22-IRF4 rearrangement (<5%)	CD4-, CD8+ or CD4-, CD8-	Transformed MF

LyP: lymphomatoid papulosis; MF: mycosis fungoides; C-ALCL: cutaneous anaplastic large cell lymphoma.

Table 3. Characteristic clinical and immunophenotypic features of various types of CTCL.

	Clinical features	T-cell phenotype	Cytotoxic proteins	CD56	Major lineage	EBV
Mycosis fungoides	Patches and plaques; (ulcerating) tumors in advanced stage	CD3+, CD4+, CD8-	-	-	αβ T-cell	-
C-ALCL	Solitary or localized nodules or tumors	CD3+/-, CD4+, CD8-, CD30+	+	-	αβ T-cell	-
SPTCL	Subcutaneous nodules and plaques	CD3+, CD4-, CD8+	+	-	αβ T-cell	.
PCGD-TCL	Ulcerating plaques and tumors	CD3+, CD4-, CD8+	+	+	γδ T-cell	-
Extranodal NK/T-cell lymphoma	(Ulcerating) plaques and tumors	CD3+, CD4-, CD8+ (surface CD3 -)	+	+	NK or γδ T-cell	+
CD8+ AECTCL	Ulcerating plaques, nodules and tumors	CD3+, CD4-, CD8+	+	-	αβ T-cell	-
Primary cutaneous acral CD8+ T-cell lymphoma	Solitary papule or nodule on acral site (ear; nose)	CD3+, CD4-, CD8+	+/-*	-	αβ T-cell	-
Primary cutaneous CD4+ small/medium T-cell LPD	Solitary nodule or tumor on the face or upper trunk	CD3+, CD4+, CD8-, CD279/PD-1+	-	-	αβ T-cell	-

SPTCL: subcutaneous panniculitis-like T-cell lymphoma;

PCGD-TCL: primary cutaneous γ/δ T-cell lymphoma

CD8+ AECTCL: primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

MF: mycosis fungoides; C-ALCL: cutaneous anaplastic large cell lymphoma;

* Expresses a non-activated cytotoxic phenotype, positive for TIA-1, but negative for other cytotoxic proteins.

Table 4. Characteristic features of PCFCL with a diffuse growth pattern and PCLBCL, leg type

	PCFCL, diffuse large cell	PCDLBCL, leg type
Clinical presentation	Localized skin lesions on head or trunk; multifocal lesions in rare cases	Skin tumors on (lower) leg(s); uncommonly, lesions at other sites than the leg (15%)
Histopathology		
Morphology tumor cells	Predominance of large centrocytes; centroblasts may be present, but not in confluent sheets	Predominance or confluent sheets of centroblasts and/or immunoblasts
Admixed T-cells	Often abundant	Sparse, mainly perivascular.
Immunohistochemistry		
B-cell lineage markers	CD20+, CD79a+, PAX5+, IgM-, IgD –	CD20+, CD79a+, PAX5+, IgM+, IgD+/-; monotypic light chain expression
Germinal center markers	BCL6+, BCL2-, CD10-	BCL6+/-, BCL2+, CD10-
Post-germinal center markers	IRF4/MUM1-, FOXP1-	IRF4/MUM1+, FOXP1+
MYC expression	negative	Positive (65-80%)
CD21/CD35: (remnants) of FDC networks	Sometimes present	absent
Molecular genetics		
Gene expression profile	GCB-type DLBCL	ABC-type DLBCL
Translocations *BCL6*, *MYC*, *IgH*	Absent	*BCL6* (30%), *MYC* (35%), *IgH* (50%)
Array-based CGH; FISH	amplification 2p16.1 deletion 1p36 deletion 14q11.2-q12	deletion 6q arm (*BLIMP1*:60%) deletion 9p21.3 (*CDKN2A*:67%)
NF-kB pathway mutations	no *MYD88* mutation	MYD88 (60%), CD79B (20%), CARD11 (10%), TNFAIP3/*A20* (40%),
Treatment and clinical course		
First-line of therapy	Radiotherapy	R-CHOP
Relapse rate	30%	70%
Extracutaneous dissemination	10%	45%
Prognose	5-year survival 95%	5-year survival 50-60%

PCFCL: primary cutaneous follicle center lymphoma; PCDLBCL: primary cutaneous diffuse large B-cell lymphoma; FDC: follicular dendritic cell.

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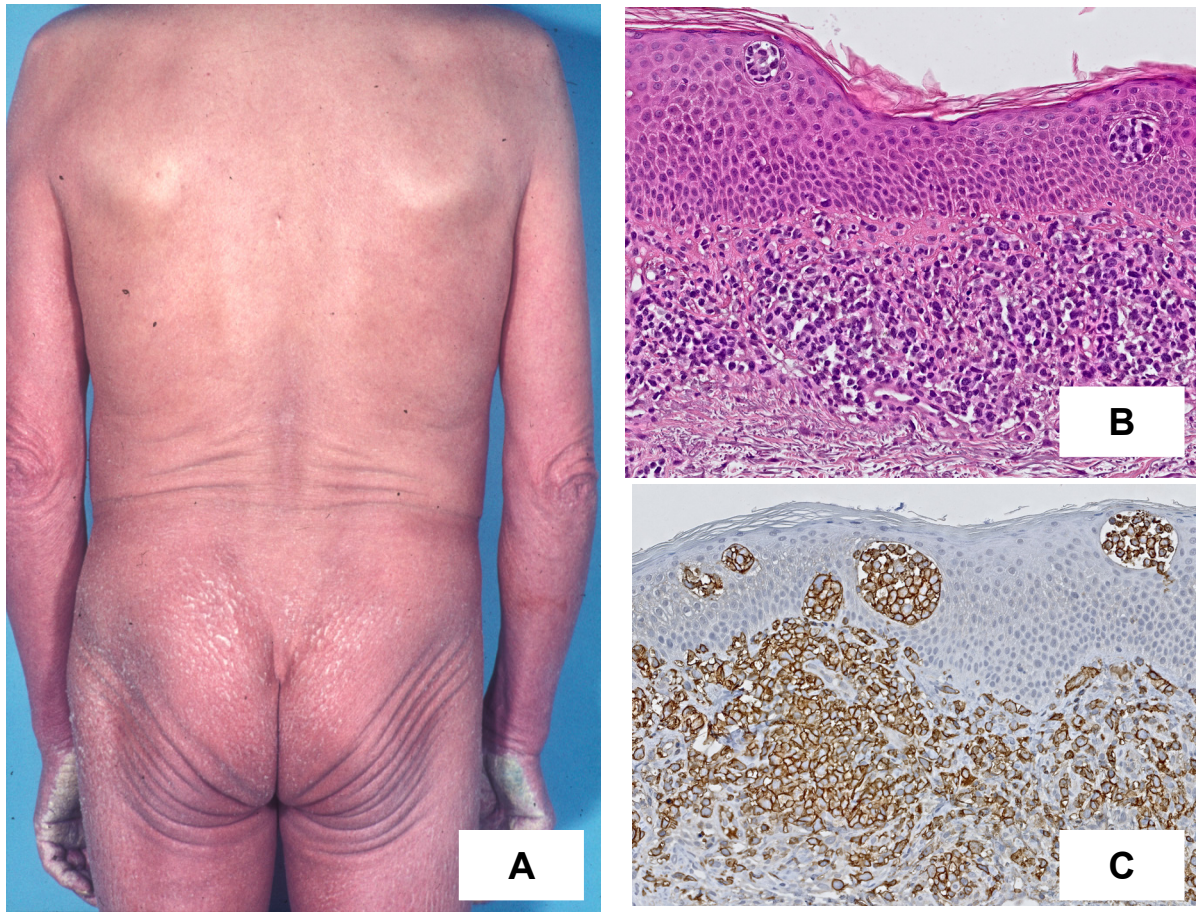

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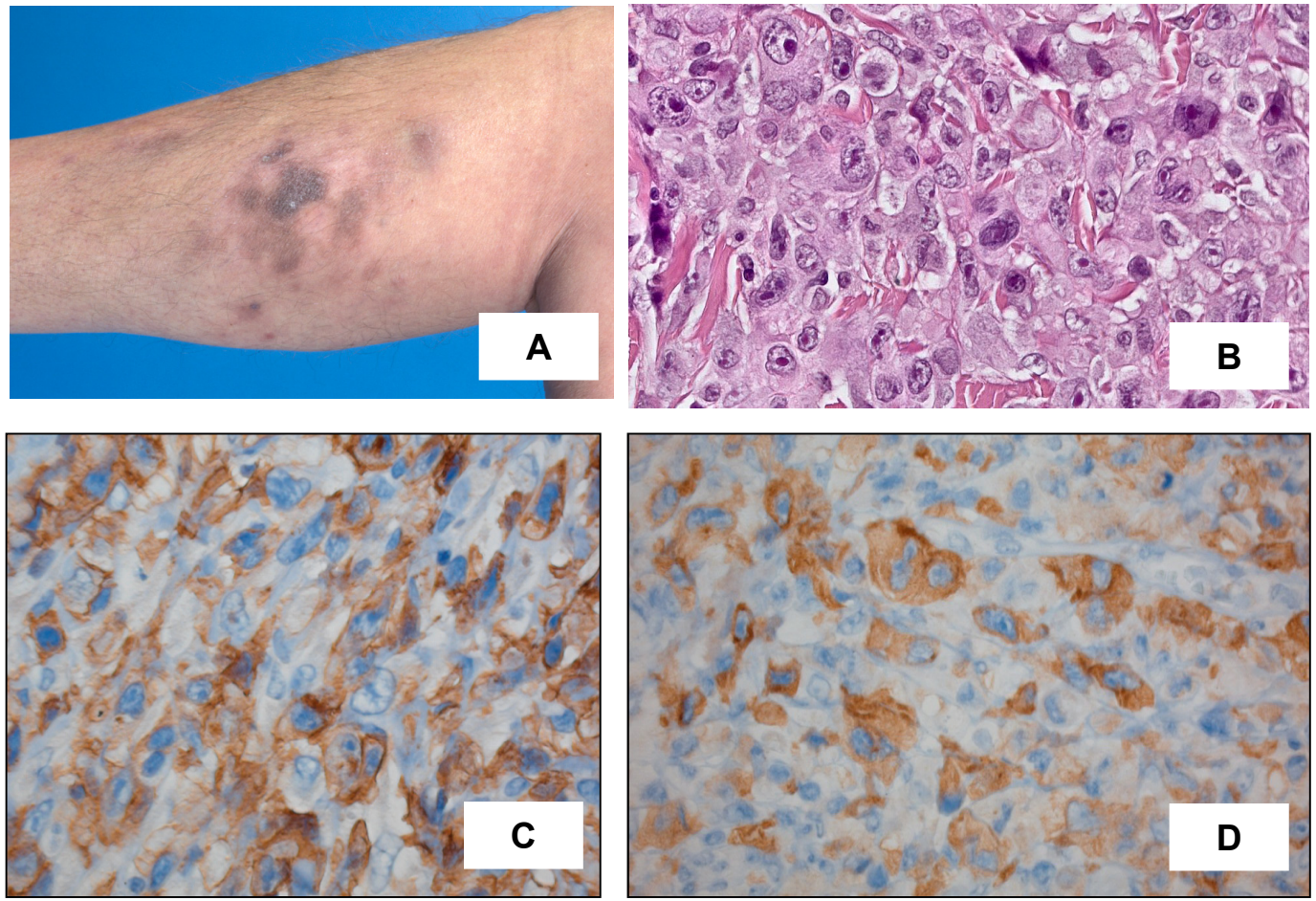
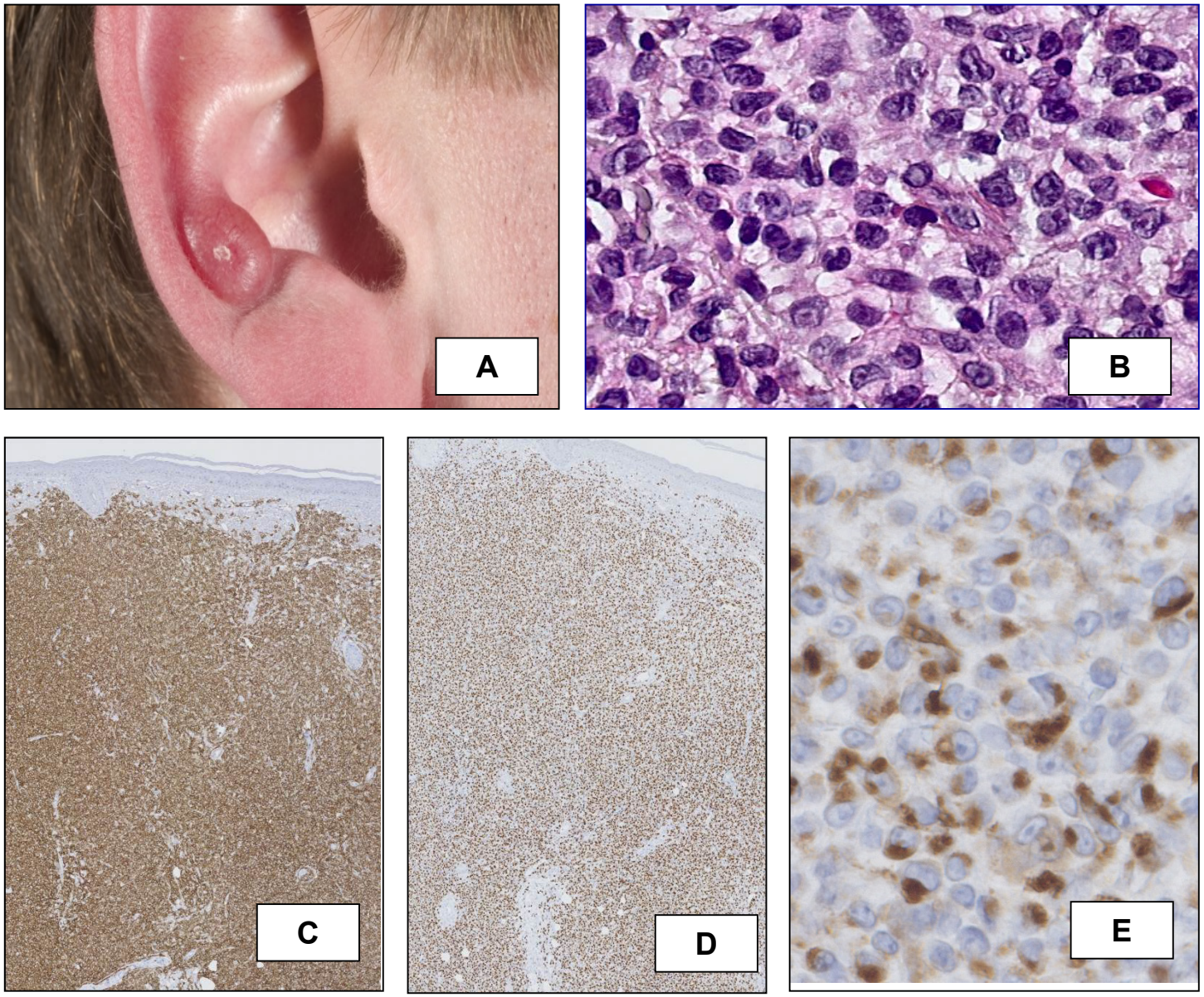


Fig. 2.

Fig. 3.



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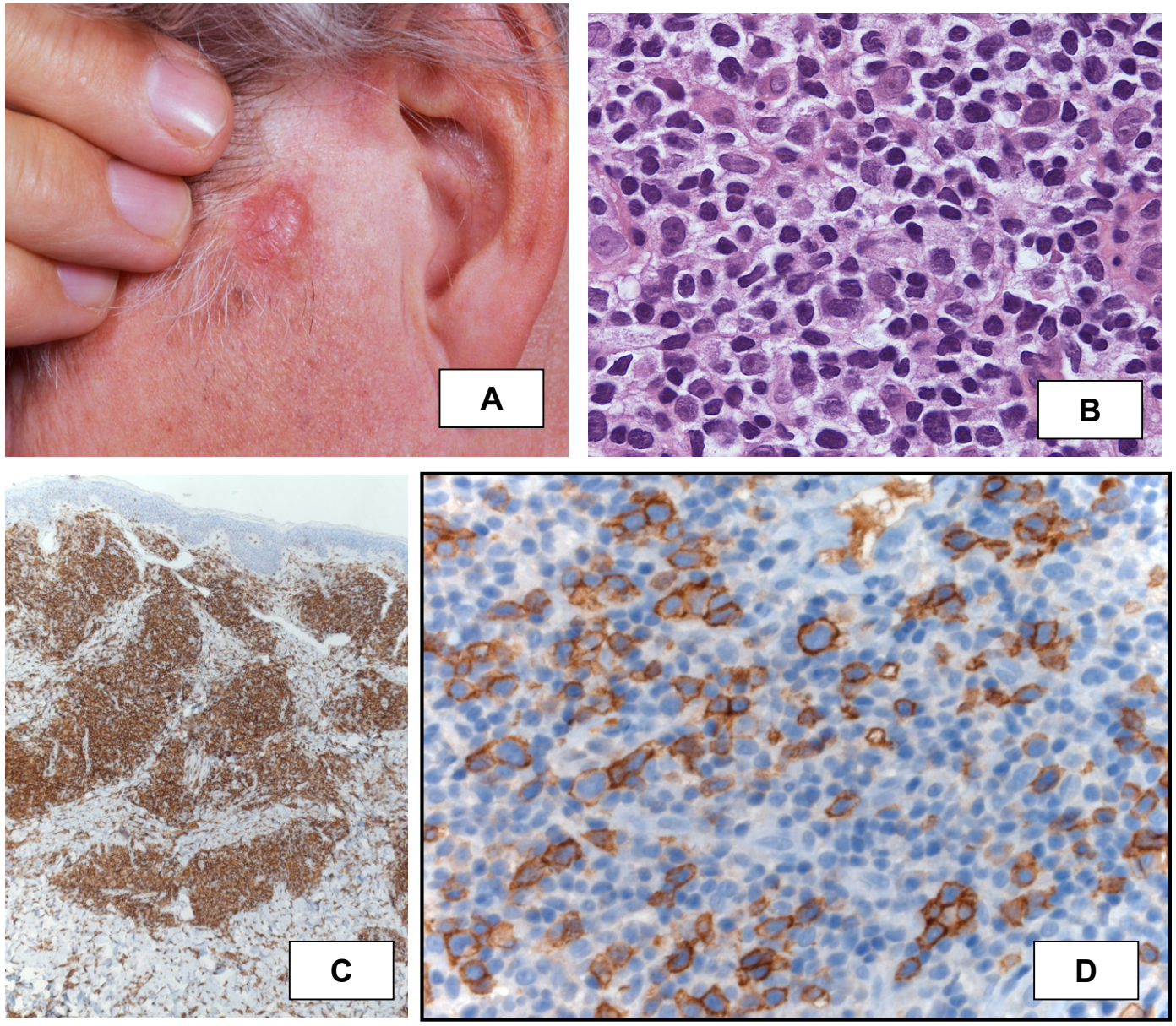

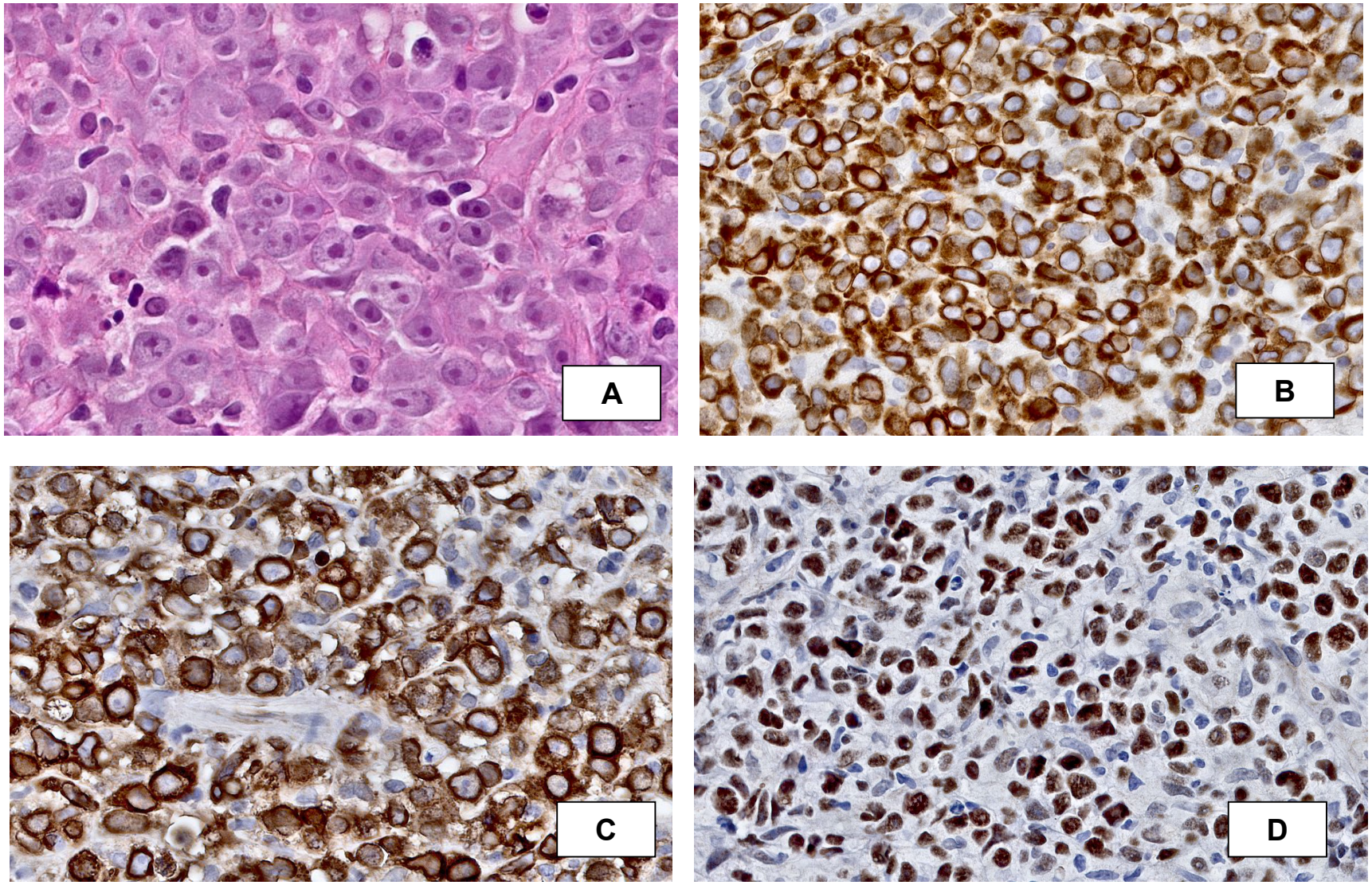

Fig. 5.

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The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas

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