Primary cutaneous lymphomas. Diagnostic and therapeutic guidelines of the Polish Dermatological Society (PTD) and Polish Lymphoma Research Group (PLRG)

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Dermatol Rev/Przegl Dermatol 2023, 110, 647–674
DOI: https://doi.org/10.5114/dr.2023.138937

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ABSTRACT

Primary cutaneous lymphomas are a heterogeneous group of rare lymphoproliferative diseases that are initially limited to the skin but potentially also involve the lymph nodes, blood, and occasionally visceral organs. They develop from mature T cells, B cells, and NK cells. The classification includes a wide range of pathologies, each characterized by distinct clinical symptoms and variations in disease course. Cutaneous lymphomas are typically chronic in nature, and a complete cure is rarely achievable. Since primary cutaneous lymphomas are uncommon and present in many variants, they pose diagnostic and therapeutic challenges that require multidisciplinary collaboration between dermatologists, pathologists, hematologists, and oncologists. We present revised guidelines for the diagnosis and treatment of primary cutaneous lymphomas, with the goal of simplifying the diagnostic and therapeutic procedure in routine clinical practice. The guidelines cover the clinical, histopathological, and dermoscopic characteristics of skin lesions, along with recommendations for the diagnostic and therapeutic management of primary cutaneous lymphomas. When selecting the most suitable therapeutic approach for individual patients diagnosed with primary cutaneous lymphoma, the main factor to consider should be the clinical stage of the disease. However, other factors, such as the patient's age, overall health, and medical history, should also be taken

into account. The choice of therapy should be guided by finding optimal efficacy and safety. The guidelines also include globally recognized therapeutic approaches that are currently not accessible in Poland. The recommendations rely on the existing Polish and global guidelines, and the knowledge and experience of experts.

Key words: diagnosis, treatment, recommendations, mycosis fungoides, primary cutaneous lymphomas.

DIAGNOSTIC STANDARDS

Primary cutaneous T-cell lymphomas (pCTCL) and primary cutaneous B-cell lymphomas (pCBCL) exhibit a different clinical course, each requiring specific diagnostic management. The diagnosis of cutaneous lymphoma and the classification of its type should be based on a combination of clinical features, histopathological examination of a biopsy specimen of the skin, the lymph node (excisional biopsy) or, less commonly, another involved body organ, immunophenotyping, and genetic testing (necessary for certain lymphoma types). The diagnostic workup outlined above enables lymphoma classification into a specific histopathological subtype following the criteria set out by the World Health Organization (WHO) [1]. The WHO/EORTC (WHO/European Organization for Research and Treatment of Cancer) classification of cutaneous lymphomas is shown in table 1.

The first step in diagnosing clinically suspicious lesions involves obtaining a skin specimen, typically from the most representative focal infiltrate, if only one biopsy is performed. In certain situations, however, multiple biopsies should be taken (according to the National Comprehensive Cancer Network [NCCN] Guidelines: when there is no histopathological confirmation of CTCL, when large cell transformation (LCT) or folliculotropism is suspected, and in patients with an aggressive clinical course). Where lesions exhibit significant morphological diversity, collecting skin specimens for examination from each morphological type of lesion is recommended. If this is not feasible, biopsy should be obtained from the lesion with the most significant infiltration. Discontinuation of skin-directed therapy at least 2–3 weeks before skin biopsy is recommended to facilitate histopathological diagnosis.

In patients with the most common type of lymphoma, mycosis fungoides (MF), imaging assessment in early MF (stages IA and IB with limited skin involvement and no signs of lymphadenopathy on physical examination or visceral involvement) is regarded as optional. However, the authors recommend diagnostic imaging, as it is essential for precisely establishing the N and M criteria. It is important to note that MF and lymphomatoid papulosis (LyP) are associated with a higher risk of other concomitant malignancies, and without imaging findings their diagnosis may be delayed [2]. In patients at disease stages other than IA and IB, computed tomography (CT) imaging of the head, neck, thorax, abdomen, and pelvis, or positron emission tomography (PET) are recommended to accurately determine TNM staging.

In MF stages IA–IIA, bone marrow examination (aspiration biopsy and trephine biopsy) is deemed unnecessary. However, peripheral blood smear test and peripheral blood immunophenotyping is justified to distinguish advanced from early stages, as the presence of cancer clone has an adverse effect on prognosis. The loss of CD26 expression in over 30% of CD4+ cells and/or the absence of CD7 expression in over 40% of cells indicates peripheral blood involvement. Similarly, a CD4/CD8 ratio greater than 10 : 1 and an absolute Sézary cell count > 1000/μl in peripheral blood are suggestive of Sézary syndrome (SS). To diagnose SS, at least one of the above-mentioned hematological criteria indicating peripheral blood involvement should be met.

CTCL can be linked to elevated blood levels of total IgE (typically < 1000) and increased lactate dehydrogenase (LDH) levels, both of which are known to be adverse prognostic factors. In cases where the diagnosis is uncertain, T-cell receptor (TCR) gene rearrangement testing should be performed for several skin specimens collected from various lesion types, lymph nodes as well as blood samples. In patients with erythroderma, skin and nasal swabs and blood smear test for bacterial isolation with antibiogram should be considered, followed by antibiotic therapy, if necessary. Despite the recognized problem of delayed diagnosis, particularly in MF, it is also important to consider the risk of overdiagnosis. The risk is linked to the possibility of obtaining a positive skin biopsy result ('lymphoma') in chronic severe inflammatory dermatoses, especially severe atopic dermatitis, and other conditions, mainly associated with CD30+ expression. In every case, the immu-

Table 1. WHO-EORTC classification of cutaneous lymphomas

Primary cutaneous T/NK-cell lymphoma
Mycosis fungoides (MF) and variants – folliculotropic – pagetoid reticulosis – granulomatous slack skin
Sézary syndrome (SS) (note: in the 5th edition of the WHO classification SS was included as mature T- and NK-cell leukemia) [4]
Primary cutaneous CD30+ T-cell lymphoproliferative disorders: – lymphomatoid papulosis (LyP) – primary cutaneous anaplastic large cell lymphoma (CALCL)
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
Primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL)
Hydroa vacciniforme-like lymphoproliferative disorder (HV-like LPD)
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL)
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
Adult T-cell leukemia/lymphoma (ATLL)
Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)
Extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT)
Primary cutaneous B-cell lymphomas
Primary cutaneous marginal zone lymphoma (PCMZL)
Primary cutaneous follicle center lymphoma (PCFCL)
Primary cutaneous large B-cell lymphoma, leg type (PCLBCL-leg type)
Intravascular large B-cell lymphoma (IVLBCL)
EBV+ mucocutaneous ulcer
Other T-cell lymphomas with common primary or secondary cutaneous involvement
Blastic plasmocytoid dendritic neoplasm (BPDCN)
Angioimmunoblastic T-cell lymphoma (AITL)
Anaplastic large cell lymphoma, ALK-positive (ALCL ALK (+))
Anaplastic large cell lymphoma, ALK-negative (ALCL ALK (–))
Breast implant-associated anaplastic large cell lymphoma

nophenotype of abnormal cells should be evaluated through immunohistochemistry or flow cytometry. These tests allow the assignment of a particular lymphoma clone to the T-cell lineage (CD2, CD3, CD4, CD5, CD7, CD8 and CD30) or B-cell lineage (CD19, CD20). In all CTCL and CBCL subtypes, the tests listed above are also essential for differentiating with extracutaneous lymphomas and determining the TNMB (tumor-node-metastasis-blood) clinical staging, which varies across different CTCL subtypes (tables 2 and 3 for MF/SS, table 4 for other CTCL types) [3, 4]. The diagnostic procedures necessary for staging encompass physical examination with evaluation of skin lesion type, skin biopsy, peripheral blood testing (including LDH), peripheral blood flow cytometry, and diagnostic imaging. In aggressive cutaneous lymphoma subtypes, the preferred method for determining the stage is PET/CT. The extent of skin lesions in adults is assessed with the Wallace rule of nines and/or the palm rule (1% of body surface area, BSA). Tables 5 and 6 present the modified Severity Weighted Assessment Tool (mSWAT) criteria for evaluating the progression/remission of skin lesions (the surface area of the patient's palm with fingers equals 1% of the body surface).

STANDARDS FOR HISTOPATHOLOGICAL DIAGNOSIS

In the majority of cases, the diagnosis of primary cutaneous lymphoma is established by a dermatologist in collaboration with a pathologist. The diagnosis relies on clinical examination, histopathological assessment of a specimen of affected skin, considering the morphology and immunophenotype of the neoplastic infiltrate, and, in warranted cases, also molecular testing. In specific cases, the assessment at diagnosis may also include the examination of lymph

Table 2. Classification of cutaneous, nodular and visceral lesions, and peripheral blood involvement in mycosis fungoides and Sézary syndrome according to the International Society for Cutaneous Lymphoma (ISCL) and European Organization for Research and Treatment of Cancer (EORTC) and TNMB (tumor–node–metastasis–blood) staging system

Skin	
T1	Limited patches*, papules, and/or plaques** covering < 10% of the skin surface
T1a	Patches only (< 10% of the skin surface)
T1b	Patches and plaques (< 10% of the skin surface)
T2	Patches, papules, or plaques covering ≥ 10% of the skin surface
T2a	Patches only (≥ 10% of the skin surface)
T2b	Patches and plaques (≥ 10% of the skin surface)
T3	One or more tumors*** (≥ 1 cm in diameter)
T4	Confluence of erythema covering ≥ 80% of body surface area

**Patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikilodermа should be noted; **Plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of the same features as for patches should be noted. Folliculotropism or large-cell transformation (> 25% large cells), CD30+ or CD30– are important to document. ***Tumor indicates a solid lesion ≥ 1 cm in diameter, with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also, note if histologic evidence listed above (CD30 expression, large-cell transformation) is present.*

Node	
N0	No clinically abnormal* peripheral lymph nodes (i.e. cervical, supraclavicular, epitrochlear, axillary, and inguinal); biopsy not required
N1	Clinically abnormal* peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0–2
N1a	Clone negative**
N1b	Clone positive**
N2	Clinically abnormal* peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative**
N2b	Clone positive**
N3	Clinically abnormal* peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN4; clone positive or negative**
Nx	Clinically abnormal* peripheral lymph nodes; no histologic confirmation

**Abnormal peripheral lymph node indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or ≥ 1.5 cm in diameter. Pathological central nodes, which are not amenable to pathologic assessment, are not currently considered in the nodal classification; **T-cell clonality is determined by polymerase chain reaction (PCR) or Southern blot analysis, evaluating clonality of the TCR gene rearrangement*

	Histopathological staging of lymph nodes	
ISCL/EORTC (TNMB) classification	**Dutch system**	**NCI-VA**
N1	Grade 1: dermatopathic lymphadenopathy (DL)	LN0: no atypical lymphocytes LN1: occasional and isolated atypical lymphocytes (not arranged in clusters) LN2: many atypical lymphocytes or in 3–6 cell clusters
N2	Grade 2: DL; early involvement by MF (presence of cerebriform nuclei > 7.5 μm)	LN3: aggregates of atypical lymphocytes; nodal architecture preserved
N3	Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells (CMCs) Grade 4: complete effacement of LN architecture	LN4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells
	Visceral organs	
M0	No visceral organ involvement	
M1	Visceral involvement (must have pathology confirmation* and organ involved should be specified)	
**Spleen and liver may be diagnosed by imaging criteria.*		
	Blood	
B0	Absence of significant blood involvement or ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells	
B0a	Clone negative*	
B0b	Clone positive*	
B1	> 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2	
B1a	Clone negative*	

B1b	Clone positive*
B2	≥ 1000/μl atypical (Sézary) cells with positive clone**

**T-cell clonality is determined by polymerase chain reaction (PCR) or Southern blot analysis, evaluating clonality of the TCR gene rearrangement; **For peripheral blood, Sézary cells are defined based on the morphological features of cell nuclei (hyperconvoluted, cerebriform). If the Sézary cell count cannot be determined, then modified ISCL criteria may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of > 10; or (2) expanded CD4+ cells with abnormal immunophenotype (i.e. with loss of CD7 or CD26).*
MF – mycosis fungoides, NCI – National Cancer Institute, NCI-VA – National Cancer Institute–Veterans Affairs, PCR – polymerase chain reaction, TCR – T-cell receptor.

nodes or specimens obtained from other involved organs. Skin biopsy from the abdomen should be avoided (unless it is the sole location of skin lesions), similarly to seborrheic areas and necrotic lesions. These body locations are statistically more prone to exhibiting atypical histopathological features, even with a meticulously performed examination (40–50% of early MF and SS stages). The biopsy site can be selected after dermoscopic assessment of skin lesions (a detailed description of cutaneous manifestations of MF is provided at the end of the Guidelines). In patients with lymphadenopathy, the entire lymph node or a wedge biopsy specimen should be submitted for evaluation of the degree of effacement of nodal architecture by potential neoplastic infiltration. In cases where accessing a lymph node for diagnosis is challenging, a combination of core needle biopsy and fine needle aspiration biopsy, along with cytometry and molecular tests, can be used. In all cases, immunophenotypic assessment of anomalous cells should be performed either on sectioned tissue samples by immunohistochemistry or in a cell suspension by flow cytometry.

The recommended immunophenotypic panel for diagnosing T/NK-cell lymphomas encompasses the following antibodies: CD2, CD3, CD4, CD5, CD7, CD8, cytotoxic granule proteins (granzyme B, perforin, TIA1), CD30, CD56, CD16, ALK1, EBV-LMP1/EBER-ISH, CD25, bF1, TCRß, TCRδ. The supplementary immunophenotypic panel, comprising CCR4, CXCL13, ICOS, and PD-1, is particularly useful in the differential diagnosis with the recently described primary cutaneous T-follicular helper (TFH) lymphoma, among others [5, 6]. This lymphoma, classified as a variant of PTCL-NOS, is clinically evident through a sudden appearance of plaques and nodules exhibiting the expression of follicular helper T-cell markers. Since clinical characteristics are similar to MF, determining the phenotype by histopathological examination is crucial in the differential diagnosis [7, 8]. For diagnosing B-cell lymphomas, a panel containing CD19, CD20, Ki-67, CD5, CD43, CD21, CD23, cyclin D1, CD138, kappa/lambda, CD10, Bcl6, BCl2, MUM1, and EBV-LMP1/EBER-ISH is recommended. Immunophenotypic differential diagnosis of cutaneous T-cell and B-cell lymphomas according to the NCCN Guidelines (version 1.2023 of 5 January 2023) is shown in figs. 1–3. In doubtful cases, these tests may be complemented by a more comprehensive and specific panel of monoclonal antibodies, along with molecular tests such as TCR gene rearrangement and/or immunoglobulin heavy chain (IGH) rearrangement.

Table 3. Clinical stages and prognostic groups in mycosis fungoides and Sézary syndrome according to the International Society for Cutaneous Lymphoma (ISCL) and European Society of Research and Treatment of Cancer (EORTC)

Stage	T	N	M	Peripheral blood involvement
I				
IA	1	0	0	0, 1
IB	2	0	0	0, 1
II				
IIA	1, 2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
III				
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IV				
IVA1	1–4	0–2	0	2
IVA2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

PRIMARY CUTANEOUS T-CELL LYMPHOMAS (PCTCL)

Mycosis fungoides (MF)

Cutaneous T-cell lymphomas account for 75–80% of all primary cutaneous lymphomas, with MF recognized as the most prevalent CTCL type. MF is characterized by an indolent clinical course, with a potential involvement of lymph nodes or peripheral blood or, rarely, other visceral organs in advanced stages. The WHO-EORTC classification distinguishes several histopathological variants of MF, including folliculotropic MF (FMF), pagetoid reticulosis, and granulomatous slack skin.

MF primarily occurs in adults, with a slightly higher prevalence in men. The median age at diagnosis is 55–60 years. During the initial phase of MF (TNM stage I), patches appear, occupying < 10% BSA (fig. 4).

Table 4. ISCL/EORTC TNM classification of cutaneous lymphoma other than MF/SS

T	N	M
T1: Solitary skin involvement	**N0:** No clinical or pathologic lymph node involvement	**M0:** No evidence of extracutaneous non-lymph node disease
T1a: a solitary lesion < 5 cm diameter T1b: a solitary lesion > 5 cm diameter		
T2: Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions*	**N1:** Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement	**M1:** Extracutaneous non-lymph node disease present
T2a: all-disease-encompassing in a < 15-cm-diameter circular area T2b: all-disease-encompassing in a > 15- and < 30-cm-diameter circular area T2c: all-disease-encompassing in a > 30-cm-diameter circular area	**N2:** Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region** that does not drain an area of current or prior skin involvement	
T3: Generalized skin involvement		
T3a: multiple lesions involving 2 noncontiguous body regions T3b: multiple lesions involving ≥ 3 body regions	**N3:** Involvement of central lymph nodes	

**Definition of body regions (see the figure in the reference study [Kim et al. 2007]. **The definition of peripheral and central lymph node regions is consistent with the Ann Arbor system; peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal; central sites: mediastinal, pulmonary hilar, paraortic, iliac.*
ISCL/EORTC – International Society for Cutaneous Lymphoma (ISCL) and European Organization for Research and Treatment of Cancer (EORTC).

Table 5. Modified Severity Weighted Assessment Tool (mSWAT) criteria and evaluation of the progression/remission of skin lesions (the surface area of the patient's palm with fingers equals 1% of the body surface)

Body region	BSA in body region (%)	Assessment of involvement in patient's skin		
		Patch*	Plaque**	Tumor***
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion (% BSA)	100	A	B	C
Weighting factor	NA	×1	×2	×4
Subtotal of lesion (% BSA) × weighting factor	NA	A × 1	B × 2	C × 4

**Patch indicates any size skin lesion without significant elevation or induration. Poikiloderma should be noted; **Plaque indicates any size skin lesion that is elevated or indurated. Presence of crusting, ulceration and poikiloderma should be noted; ***Tumor indicates at least one ≥ 1 cm diameter solid lesion with evidence of depth and/or vertical growth. For erythroderma, only patch and plaque columns should be included in assessment. mSWAT score equals summation of each column line: mSWAT = [(A × 1) + (B × 2) + (C × 4)]; % BSA – % body surface area; NA – not applicable.*

They are most commonly located on covered areas of the trunk and buttocks. In MF stages IB–IIA, plaques within and beyond patches predominate (fig. 5). Skin lesions may become generalized, ultimately covering over 80% of the BSA (erythroderma, MF III, fig. 6). MF IIB nodular stage is characterized by the presence of tumors (fig. 7) with a tendency towards ulceration and disintegration. In advanced stages (MF stage IV), lymph nodes and occasionally visceral organs are involved. A distinctive feature of MF is the

Table 6. Assessment of treatment response based on skin condition according to the modified Severity Weighted Assessment Tool (mSWAT) criteria

Definition	Response
Complete response (CR)	100% clearance of skin lesions*
Partial response (PR)	50–99% clearance of skin disease from baseline without new tumors (T3) in patients with T1, T2 or T4 (only skin disease)
Stable disease (SD)	< 25% increase or < 50% clearance in skin disease from baseline without new tumors (T3) in patients with T1, T2, or T4 (only skin disease)
Progressive disease (PD)**	> 25% increase in skin disease from baseline, or new tumors (T3) in patients with T1, T2, or T4 (only skin disease), or loss of response: in patients with CR or PR increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with CR

**Skin biopsy is not required. Skin biopsy with histopathology is necessary if there are doubts about skin lesion clearance (persistent patches, hyperpigmentation not due to active disease) – if histopathological signs or suspicions of MF/SS are present, assess as partial response (PR); **whichever occurs first.*

concurrent presence of all types of skin eruptions, manifesting as the disease progresses over the years. The prognosis of MF varies, depending on the disease stage and subtype, the extent of skin lesions, and the presence of lymph node and/or visceral organ involvement. In MF stages IA and IB the 5-year survival rate is 95.2% and 83.9%, respectively. Patients with MF stage IIA have a 5-year survival rate of 68.3%. In advanced stages, 45.9% of patients survive 5 years in MF stage IIB, 62.8% in IIIA, 44.6% in IIIB, 45.9% in IVA1, 29.9% in IVA2, and 36.5 % in IVB [9].

Awareness of various histopathological variants can be helpful in the diagnostic process. Skin lesions may be hyper- or hypopigmented; folliculotropic MF (fig. 8) is characterized by dense infiltration around hair follicles in sun-exposed areas such as the head and neck, frequently associated with alopecia and pruritus, which serve a measure of disease activity; solitary pagetoid reticulosis and CD8+ MF variants typically have an indolent course; and granulomatous slack skin is a rare variant which is manifested clinically by sagging skin folds with a predilection towards the axilla and the groin. Attention should also be given to MF with large cell transformation (LCT), defined as the presence of large cells (> 4 times the size of normal cells; CD30+ or CD30−, comprising greater than 25% of the infiltrate or forming clusters of large cells seen on histopathological examination). CD30 expression can be observed but its presence is not part of the definition of LCT. MF-LCT is not included in the WHO-EORTC classification. LCT can occur regardless of disease stage but it is more commonly observed in advanced stages (1% in early stages compared to 27% in stage IIB and 56–67% in stage IV) [10, 11]. LCT is frequently, but not always, a prognostically unfavorable factor. Other adverse prognostic factors in MF include age over 60 years, elevated LDH level in peripheral blood, CD30+ < 10%, MF-LCT in the skin or lymph nodes at diagnosis, extensive skin lesions, extracutaneous MF-LCT (lymph node involvement), and advanced MF-LCT stage [1, 12–19].

In the initial stages of mycosis fungoides, the histopathological features may mimic those of chronic inflammation. Over time, subepidermal infiltrates appear, consisting of small to medium-sized T cells with cerebriform nuclei, partially penetrating the epidermis (epidermotropism), and forming Pautrier's microabscesses (or, more precisely, Darier's nests, named after the scholar who first described them). The typical MF/SS phenotype comprises CD2+, CD3+, CD4+, CD5+, CD7-, CD8- (rarely CD8+), CD30+, cytotoxic granules (–), TCR beta+, and TCR gamma–. In MF stage IIB, the infiltrates composed of cancerous lymphocytes are more dense and involve deep dermal layers, occasionally together with the subcutaneous tissue. Late-stage MF may present with the loss of antigenic characteristics of T cells and the emergence of CD30 antigen expression. When establishing a diagnosis, a minimum of two skin specimens should be obtained for histopathological examination. The histopathology report should provide details on large-cell transformation and folliculotropism. This information is crucial for guiding therapy decisions and assessing prognosis. The recommended immunohistochemical panel in cases of suspected MF comprises surface antigens: CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30. CD30 should be examined in all patients with MF/SS, especially in cases with histological evidence of large-cell transformation. The CD30 antigen can be determined either at the time of diagnosis or later, when adjusting the treatment plan. In some cases, expanding the immunohistochemistry panel to incorporate antibodies including CD25, CD5, TIA1, granzyme B, TCR beta, and TCR delta can be useful in the differential diagnosis with other lymphomas.

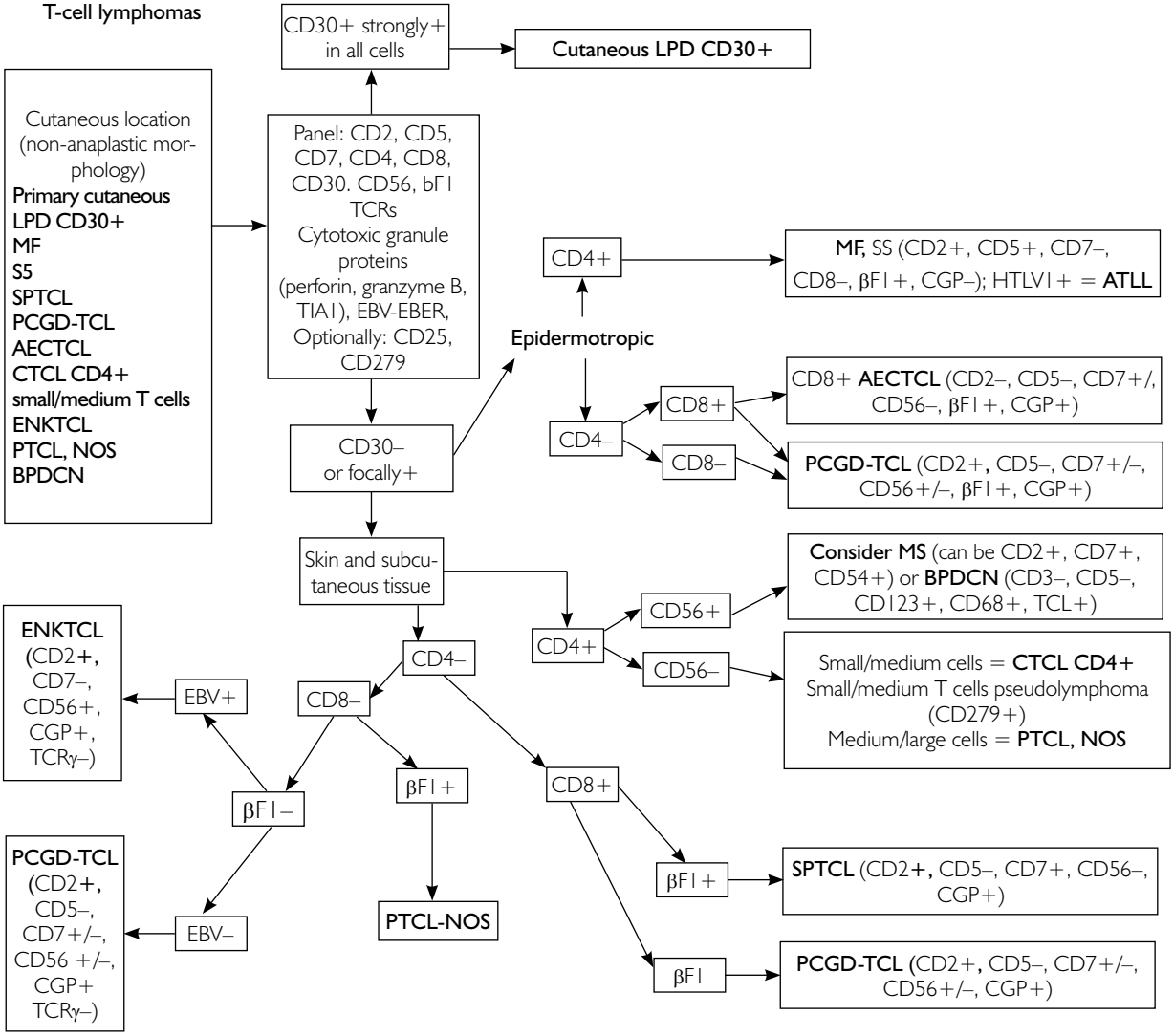

Figure 1. Immunophenotypic differential diagnosis of cutaneous T-cell lymphomas according to the National Comprehensive Cancer Network (based on www.nccn.org) (figure derived from Takeda handbook "Primary cutaneous T-cell lymphomas"). Immunophenotypic findings should be interpreted in alignment with the clinical presentation and morphological features of lymphomas (based on www.nccn.org)

AECTCL – primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, ATLL – adult T-cell leukemia/lymphoma, BPDCN – blastic plasmacytoid dendritic cell neoplasm, CGP – cytotoxic granule proteins, CTCL CD4+ – cutaneous T-cell lymphoma CD4+, ENKTCL – extranodal NK/T-cell lymphoma, nasal type, LPD CD30+ – lymphoproliferative disorder of CD30+ T-cells, MF – mycosis fungoides, MS – myeloid sarcoma, PCGD-TCL – primary cutaneous gamma/delta T-cell lymphoma, PTCL, NOS – peripheral T-cell lymphoma, not otherwise specified, SPTCL – subcutaneous panniculitis-like T-cell lymphoma, SS – Sézary syndrome.

In cases where uncertainty exists, molecular testing is recommended to detect T cell clonal expansion and determine TCR rearrangements through polymerase chain reaction (PCR). Clonality can also be assessed with techniques including karyotyping, fluorescent in situ hybridization (FISH), or next-generation sequencing (NGS) to detect somatic mutations or genetic alterations. T cell clonal expansion can also be detected in peripheral blood and tissues by flow cytometry with receptor V beta antibody panels. Interpretation of clonality results requires caution, as monoclonal TCR rearrangements can occur in non-cancerous lesions. Also, the absence of monoclonal TCR rearrangements in cases where there is a strong clinical suspicion of MF or SS does not rule out the diagnosis of these conditions. Confirming consistent clonal rearrangements in multiple cutaneous locations, in the skin, peripheral blood, and/or lymph nodes, can be helpful for establishing the diagnosis, especially when lymphoma requires differentiation from inflammatory dermatoses [12, 15–17, 20, 21].

In addition to histopathological and immunohistochemical skin examinations, which are crucial in the diagnosis of MF, biopsies are also taken from

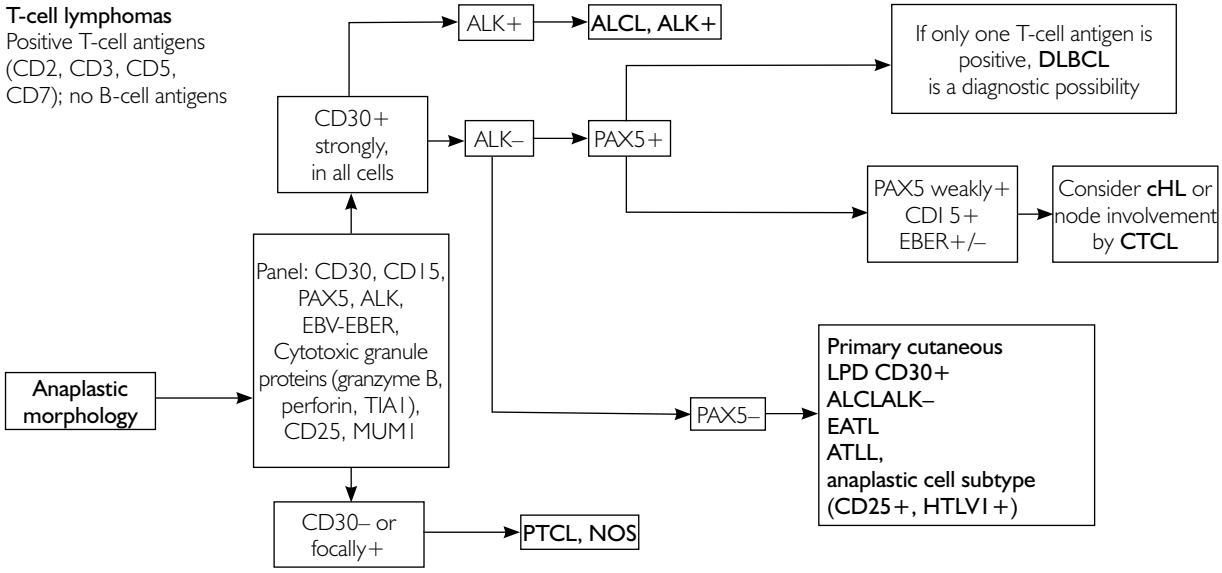

Figure 2. Immunophenotypic differential diagnosis of anaplastic T-cell lymphomas according to the National Comprehensive Cancer Network (based on www.nccn.org) (figure derived from Takeda handbook "Primary cutaneous T-cell lymphomas"). Immunophenotypic findings should be interpreted in alignment with the clinical presentation and morphological features of lymphomas (based on www.nccn.org)

ALCL – anaplastic large cell lymphoma), ATLL – adult T-cell leukemia/lymphoma), cHL – classical Hodgkin lymphoma, CTCL – cutaneous T-cell lymphoma, DLBCL – diffuse large B-cell lymphoma, EATL – enteropathy-associated T-cell lymphoma, LPD CD30+ – lymphoproliferative disorder of CD30+ T-cells, PTCL, NOS – peripheral T-cell lymphoma, not otherwise specified.

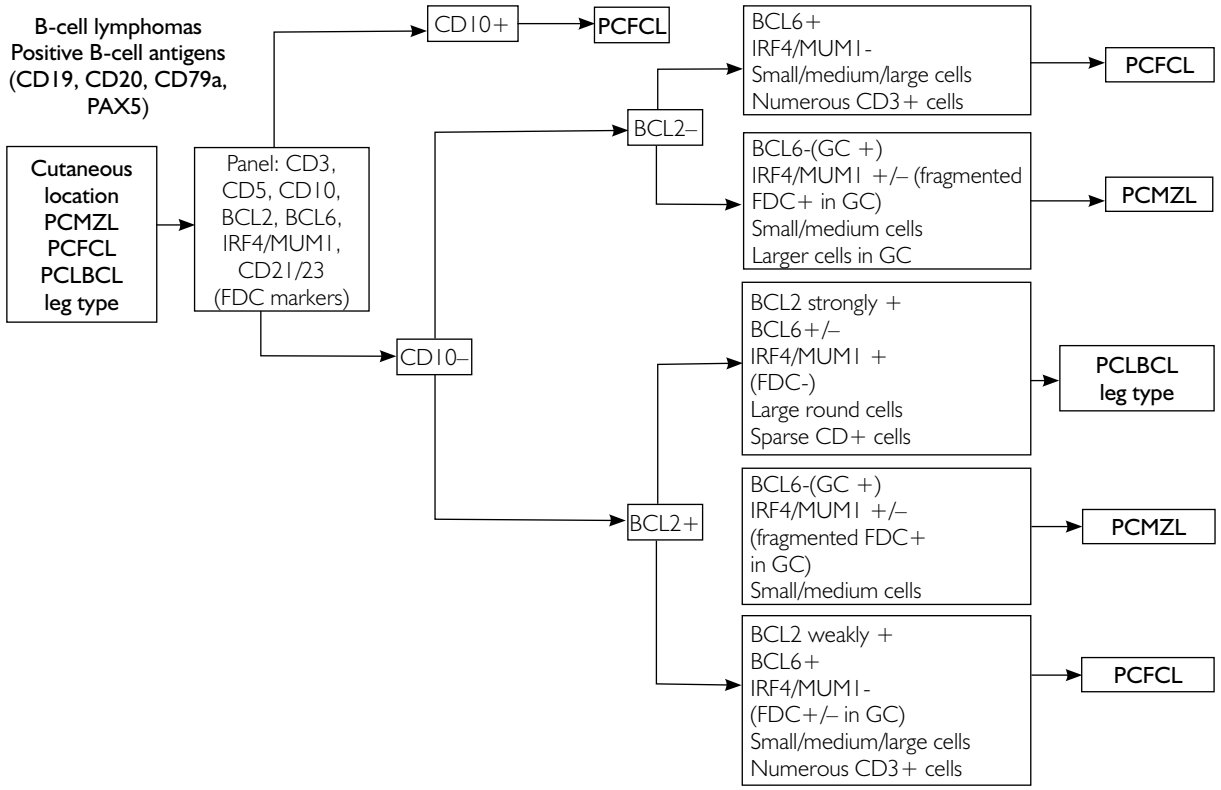

Figure 3. Immunophenotypic differential diagnosis of cutaneous T-cell lymphomas according to the National Comprehensive Cancer Network. Immunophenotypic findings should be interpreted in alignment with the clinical presentation and morphological features of lymphomas (based on www.nccn.org)

FDC – follicular dendritic cell, GC – germinal center, PCLBCL (primary cutaneous DLBCL) – primary cutaneous diffuse large B-cell lymphoma, PCFCL – primary cutaneous follicle center lymphoma, PCMZL – primary cutaneous marginal zone lymphoma).

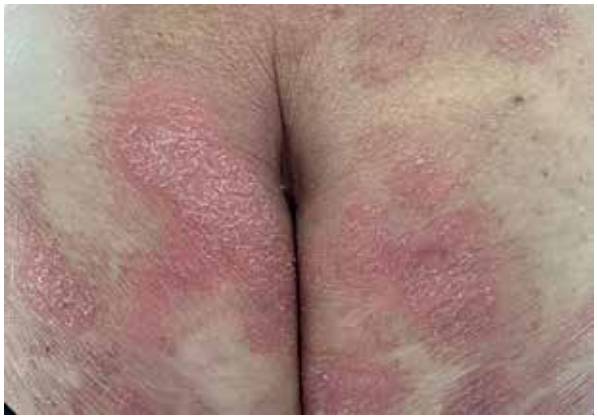

Figure 4. Early stage of mycosis fungoides – patches

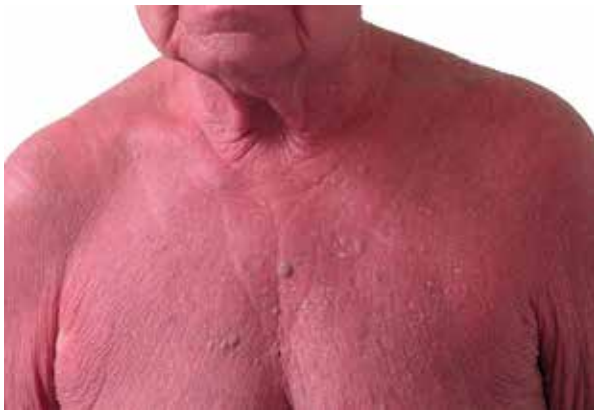

Figure 6. Erythroderma in mycosis fungoides

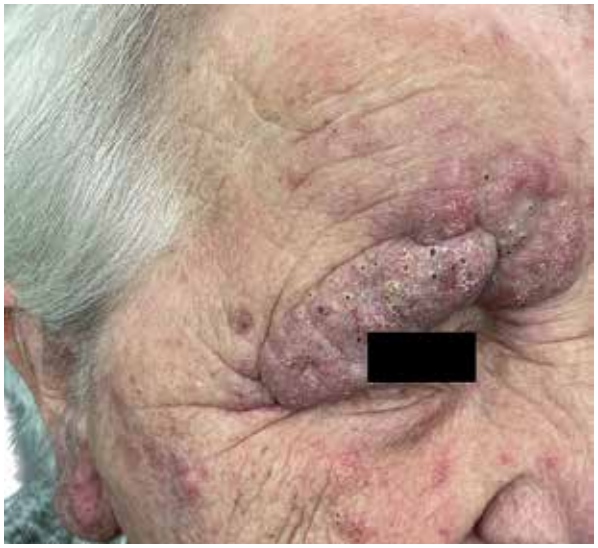

Figure 8. Folliculotropic mycosis fungoides

enlarged lymph nodes (palpable, > 1.5 cm in diameter; irregular, hard, clustered, or fixed to underlying tissue or skin) and in cases with extracutaneous localization of lymphoma. Surgical biopsy of the entire node or wedge biopsy is preferred.

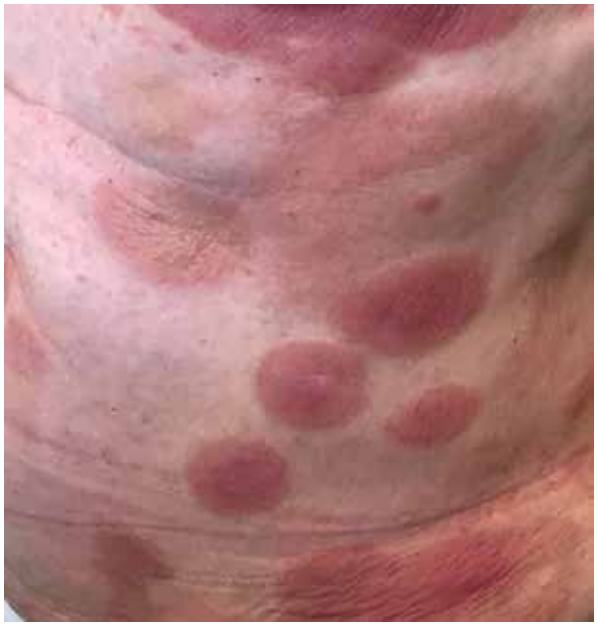

Figure 5. Plaques in mycosis fungoides

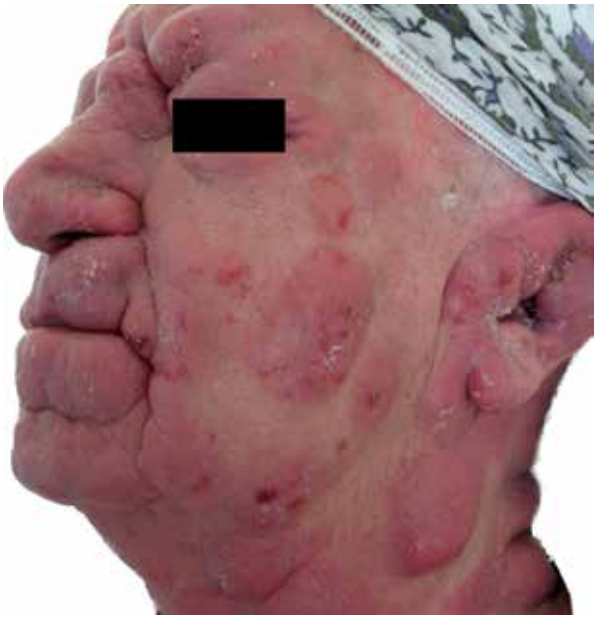

Figure 7. Tumor stage of mycosis fungoides

Evaluation of peripheral blood involvement by flow cytometry is advised for disease staging, but it is also required for differential diagnosis with other lymphomas with leukemic blood picture, such as adult T-cell lymphoma/leukemia (ATLL). Flow cytometry allows for the quantification of lymphoma cells exhibiting an abnormal phenotype (CD4 : CD8 ≥ 10, CD4+/CD26- or CD4+/CD7–). Peripheral blood evaluation also comprises peripheral blood smear test to identify Sézary cells, along with molecular testing and TCR rearrangement analysis.

Table 7. Diagnosis of MF/SS based on the 2023 NCCN Guidelines

Medical history
Skin examination: assessment of body surface area (BSA) affected and morphology of skin lesions (patches/plaques, tumors, erythroderma)
Assessment of peripheral lymph nodes and organomegaly
Biopsy of suspicious skin sites: • histopathological examination with immunophenotyping: – essential: CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30 – useful under certain circumstances: CD25, CD56, TIA1, granzyme B, TCR beta, TCR gamma, CXCL 13, ICOS, PD-1 • assessment of TCR gene rearrangement
Excisional biopsy of enlarged lymph nodes or affected organ – histopathological examination with immunophenotyping, assessment of TCR gene rearrangement
Laboratory test panel: CBC, peripheral blood flow cytometry (optional in T1), LDH, clonality assessment of TCR gene rearrangements of peripheral blood lymphocytes (recommended when peripheral blood involvement is suspected)
Contrast-enhanced CT scan of the neck, chest, abdomen and pelvis or whole-body PET/CT scan – recommended in patients with stage T3 or T4 disease (TNMB staging) and should be considered in patients with stage T2a disease (patches; ≥ 10% BSA), T2b (patches and plaques; ≥ 10% BSA), FMF, LCT, palpable adenopathy or abnormal laboratory test results

An overview of the diagnostic process in MF/SS is shown in table 7.

Sézary syndrome (SS)

SS is characterized by the concurrent presence of erythroderma, generalized lymphadenopathy, and atypical T cells with cerebriform nuclei in the skin, lymph nodes, and peripheral blood. According to the current ISCL guidelines, at least one of the following criteria must be fulfilled to diagnose SS: an absolute Sézary cell count of minimum 1000/mm^3 in peripheral blood; abnormal antigens expressed on T-cell surface, i.e. an increased CD4+ T-cell population with a shift in the CD4+/CD8+ ratio >10 and/or the loss of one or all T cell-specific antigens (CD2, CD3, CD4, CD5, CD7 and/or CD26); and evidence for T-cell clonality in peripheral blood obtained with molecular or cytogenetic methods.

Differentiating between SS and erythrodermic MF is crucial, as they represent distinct medical conditions. SS primarily affects adults, with a higher incidence in men; the median age at onset is 63 years. In the initial stages of SS, skin lesions are uncharacteristic, resembling allergic eczema. The inflammation subsequently spreads over the skin, leading to generalized erythroderma. The skin becomes thickened and red, with a tendency to scale (fig. 9). Skin lesions are accompanied by severe pruritus. Other symptoms encompass alopecia, onychodystrophy, and palmoplantar hyperkeratosis. The histological presentation shares similarities with MF, but the neoplastic infiltrate tends to be more subtle and monomorphic, frequently lacking epidermotropism. Neoplastic T cells predominantly express CD3+ CD4+ CD8–, as well as KIR3DL2/CD158k, while circulating Sézary cells in the blood are characterized by the loss of CD7 antigen (40% of cells) and CD26 antigen (30% of cells) [1, 12–15, 18, 22, 23].

Treatment of MF and SS

In patients with MF, the choice of therapy depends on disease stage. In the early stages, skin-directed therapy (SDT) is the main treatment modality. In patients with MF stage IA–IIA, treatment is primarily prescribed by dermatologists. For isolated patches, class I topical glucocorticosteroids (betamethasone

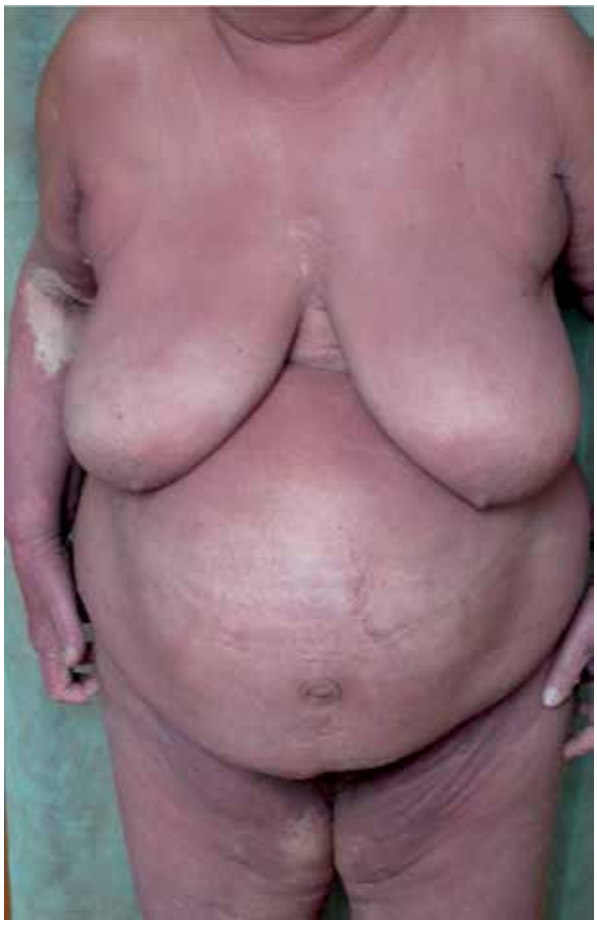

Figure 9. Thickened skin with scale in Sézary syndrome

Table 8. Radiation doses recommended in the treatment of solitary lesions according to the International Lymphoma Radiation Oncology Group Guidelines

Cutaneous lymphoma subtype	Radical treatment	Palliative treatment
Mycosis fungoides	20–24 Gy (1.8–2.0 Gy daily)	8 Gy in a single fractional dose (in patients with extensive lesions – in divided doses)
CD30+ lymphomas	20 Gy (1.8–2.0 Gy daily)	2 × 2 Gy
B-cell lymphomas	24-30 Gy (1.8–2.0 Gy daily)	4 Gy in a single fractional dose
Ultra-rare lymphomas	Selected on a case-by-case basis	Selected on a case-by-case basis

dipropionate at 0.05% or mometasone pyrosilate at 0.1%) are recommended. The minimum duration of treatment is 3 months. Other treatment options include 0.02% mechlorethamine gel or ointment applied once a day every day or 2–6 times a week, depending on skin type/development of irritant contact dermatitis as an adverse reaction (under emergency access to drug technologies (RDTL), though in the USA mechlorethamine is prescribed as first-line treatment and in Israel as second-line treatment; it has the highest degree of recommendation in the context of clinical trials; it can be combined with glucocorticosteroids to reduce the severity of adverse effects; also in combination with systemic agents), carmustine (BCNU) as an ointment or solution applied once daily, tazarotene cream or gel (off-label, currently unavailable in Poland; topical isotretinoin off-label – also in combination with topical glucocorticosteroids), imiquimod (off-label); and radiotherapy. Radiation therapy of isolated MF tumors is one of the primary methods in the treatment of localized lesions. It is also used in the therapy of anaplastic large cell lymphoma and B-cell lymphomas. Dosage varies depending on the lymphoma subtype and the desired treatment effect (radical vs. palliative dose). Basic radiation therapy doses prescribed for the treatment of isolated lesions are listed in table 8 [16, 18, 24].

Another treatment option for mycosis fungoides is total skin electron beam therapy (TSEBT), typically administered at a dose of 30–36 Gy (complete remission [CR] in 60–90% of stage T2–T4 cases; 5-year relapse-free survival at stages IB–III in 10–25% of patients). After administering a dose of 10 Gy in weekly 1 Gy fractions, response to treatment is observed in 90% of patients, including CR or VGPR (very good partial remission) in 70% of patients (< 1% of skin surface involvement by patches or plaques). The mean duration of response to treatment is 5.2 months. A lower dose provides the option to repeat radiotherapy in the event of disease relapse or progression. Following TSEBT, maintenance therapy with bexarotene or pegylated interferon α (PEG-IFN-α) is recommended.

In patients with patches and plaques covering more than 30% of the skin surface, UVB-311 nm phototherapy is recommended (also during pregnancy) for patches. UVA1 or PUVA are suggested in patients with patches/plaques or plaques. Complete renission (CR) is observed in 58–83%, and partial remission (PR) in 95% of patients. The mean duration of remission is 43 months. After achieving treatment response, phototherapy is used at a reduced frequency for an additional 2–3 months. If blood involvement (B1) is present in MF stage IA, standard treatment used in MF III can be considered. To improve the efficacy of PUVA, retinoids (acitretin, off-label isotretinoin), rexinoids (bexarotene), or PEG-IFN-α at a weekly dose starting at 90 μg, can be added in second-line treatment. Methotrexate (MTX) is a treatment option with clinically documented benefits. According to the NCCN [24] and European Society for Madical Oncology (ESMO) [17] recommendations, MTX is recommended for subsequent lines of treatment. Based on Polish publications, it is considered a viable modality for first-line therapy as well [20, 21]. Oral bexarotene at doses of up to 300 mg/m^2 is prescribed to patients with MF after unsuccessful response to another systemic therapy [1, 3, 12–18, 22]. In MF IIB, biopsy should be repeated due to the possibility of large cell transformation. In MF stages IIB–IVB without transformation, evidence suggests that the administration of chemotherapy does not result in prolonged OS. For second-line treatment of patients with MF, oral or subcutaneous MTX can be used at a weekly dose ranging from 20 to 100 mg (in three divided doses administered every 12 hours, typically 25–30 mg per week). The drug can be combined with glucocorticosteroids, PUVA, and PEG-IFN-α. In MF IIB–III, the initial approach involves PUVA in combination with bexarotene, PEG-IFN-α or MTX. These therapeutic agents can be used alone. In patients with positive CD30 expression, brentuximab vedotin (BV) is recommended for subsequent lines of treatment after the failure of previous therapies (also in MF up to stage IIA). For the MF stage IIB and higher stages, there is no requirement for prior bexarotene therapy. The efficacy of alemtuzumab (anti-CD52) remains controversial because of associated adverse effects. CR was not achieved in phase I and II clinical trials in patients treated with duvelisib (NCT02567656), everolimus (NCT01637090), and forodesine (NCT00501735), approved by the European

Medicines Agency (EMA) as an orphan drug, or lenalidomide (NCT00466921) [19, 24–28].

Given the absence of curative options for patients with MF, except for allogeneic hematopoietic cell transplantation, it is important to consider patients' participation in clinical trials before introducing systemic chemotherapy. Classical chemotherapy can be used when pegylated interferon, methotrexate, bexarotene, and brentuximab vedotin have been used without significant improvement. The recommended medications include gemcitabine and liposomal doxorubicin. These agents are also prescribed for first-line treatment in stage IV patients. Chlorambucil, etoposide, and cyclophosphamide are also considered acceptable therapeutic options. The duration of treatment varies based on efficacy and tolerability. For patients with rapidly progressing MF, gemcitabine (six cycles of 1200 mg/m^2 *i.v.* per week) or liposomal doxorubicin (40 mg/m^2 *i.v.* per month) is recommended. Treatment with liposomal doxorubicin elicits a response in 56% of patients, but with a progression-free survival (PFS) of only 5 months. Pegylated liposomal doxorubicin, at a dose of 20 mg/m^2 *i.v.* once a month, contributes to achieving CR and PR in 88% of patients. The combination of gemcitabine with bexarotene does not result in a superior therapeutic response compared to gemcitabine alone. Bexarotene therapy introduced after liposomal doxorubicin was not found to extend the remission period or increase the efficacy of the first drug (phase II trial, NCT00255801) [1, 13–17, 25].

Multidrug chemotherapy is not generally recommended, but it may be used as one of the last therapeutic options in patients who have failed to respond to previous treatments or have advanced lymphadenopathy and/or involvement of visceral organs (IVA–IVB), requiring rapid reduction of tumor mass. Polychemotherapy regimens, such as CHOP, EPOCH, and ESHAP, are known to induce a short-term response, typically lasting for several weeks. Purine base analogues and polychemotherapy in patients with CTCL are associated with an increased risk of infection and death. In young patients with stage III-IV MF, in good general condition, after unsuccessful treatment with PEG-IFN-α and bexarotene, allogeneic hematopoietic stem cell transplantation (allo-HSCT) should be considered before initiating cytostatic therapy. The procedure, combined with standard conditioning, leads to complete remissions.

When CD30 expression is present, especially in cases of large-cell transformation, the recommendation is to prescribe BV. The recommended dosage is 1.8 mg/kg/day administered intravenously every 3 weeks. Dose adjustments may be necessary based on factors such as liver failure, kidney failure, etc. as specified in the Summary of Product Characteristics (CHPL). In the ALCANZA study (NCT01578499) in patients with CTCL (BV vs. investigator's choice: MTX or bexarotene), evidence was obtained for the superiority of BV in MF (objective global response lasting at least 4 months (ORR) 50% vs. 10%), with a progression-free survival (PFS) of 15.9 months *vs* 3.5 months after a follow-up of 17.5 months [1, 12–15, 17, 22].

BV, mogamulizumab, vorinostat and romidepsin are approved by the FDA for the treatment of MF and SS. Denileukin diftitox, histone deacetylase inhibitors (HDACi): depsipeptide/romidepsin, vorinostat, belinostat as well as mogamulizumab (anti-CCR4 monoclonal antibody), have been approved by the Food and Drug Administration (FDA), European Medicines Agency (EMA) or Pharmaceuticals and Medical Devices Agency (PMDA) for the second and subsequent lines of treatment of MF patients. The MAVORIC trial (NCT01728805) demonstrated the superiority of mogamulizumab (1 mg/kg administered every week for 4 weeks, followed by every 2 weeks) compared to vorinostat (400 mg/day). The objective response rate was reported as 21% for mogamulizumab versus 4% for vorinostat. Mogamulizumab showed the highest efficacy in cases with blood involvement. In 2018, both the FDA and EMA granted approval for mogamulizumab in the treatment of CTCL after the failure of at least one prior systemic therapy. A phase II clinical trial (NCT2953301) evaluating maintenance treatment with resminostat in patients with MF IIB-IV/SS is approaching completion. Pralatrexate is another available therapeutic agent, used in refractory MF stages IIB-IV (ORR 45%, predominantly PR) and MF-LCT (ORR 58%) 15 mg/m^2/week for 3 weeks, followed by a 1-week break before the next cycle. Results from a phase I/II study (NCT01134341) showed that prelactrexate administered at a dose of 15 mg/m^2/week exhibited low toxicity. The ORR was reported as 60%. The combination is approved for the treatment of CTCL by the FDA and PMDA. In a phase II clinical trial (NCT03385226) of pembrolizumab used at a dose of 2 mg/kg every 3 weeks for a total of 24 months in MF IIB-IV/SS in patients with disease progression who failed to respond to at least one therapy, ORR was achieved in 38% of patients (9 out of 24) both with MF and SS, with a long-term duration of response. Relapse was observed in patients who discontinued treatment, which suggests that maintenance therapy is necessary. According to the 2023 NCCN Guidelines, pembrolizumab is an add-on option for the treatment of MF stages IIB and III, and MF-LCT, and in cases of relapsed and refractory MF after previously failed multiple therapies. In a phase I study with nivolumab, an ORR of 15% (PR only), and median PFS of 10 weeks were achieved. A phase I

trial evaluating the combination of duvelisib with nivolumab (NCT04652960) is currently underway. Further studies are required for ibrutinib (phase I, NCT02309580), RP6530 (phase I, NCT02567656), and resimune (anti-CD3; phase II, NCT00611208), but these therapies are associated with a high risk of peritransplant complications and death. Allo-SCT with reduced myeloablative intensity is characterized by lower peritransplant mortality rates, but the duration of response to treatment may be shorter [1, 12–17, 22].

In view of the depth of infiltration, the FMF variant in its early stages may exhibit a less favorable response to skin-directed therapies like mechlorethamine and phototherapy. When the disease is limited, with isolated patches, the prognosis is favorable, and the therapy can be administered similarly to the variant without folliculotropism. In cases involving multiple lesions, phototherapy should be provided only in combination with PEG-IFN-α, retinoids (off-label), or rexinoids. The recommended treatment modality is TSEB, and for isolated tumors, radiation therapy targeted to the area of persistent lesions is advised. The therapy of choice for pagetoid reticulosis is based on the topical application of glucocorticosteroids or mechlorethamine. Another potential therapeutic modality is phototherapy. Granulomatous slack skin is a variant of MF characterized by the presence of pendulous lax skin folds in the axillae and groins, with a granulomatous infiltrate of T cells. The recommended treatment method is radiation therapy. According to the NCCN guidelines, in patients with MF-LCT the initial treatment for generalized skin lesions and extracutaneous involvement should be based on a combination of systemic therapy (BV, gemcitabine, liposomal doxorubicin, pralatrexate, romidepsin, and pembrolizumab) with topical therapy. Patients with limited MF-LCT lesions (confined to one or more T3 lesions or plaque stage IA-IIA) may undergo TSEBT with concurrent treatment of the concomitant disease, depending on the clinical stage.

In SS, the treatment of choice is systemic therapy. In line with European and international guidelines, the first-line treatment should be extracorporeal photophoresis (ECP) combined with interferon alfa or bexarotene, PUVA combined with interferon. ECP in combination with bexarotene or PEG-IFN-α yields a response in 30–80% of patients, with complete response (CR) observed in 14–25% of cases. It needs to be noted that, in addition to being recommended for the treatment of SS, ECP is also prescribed to patients in the erythrodermic stage of MF with and without peripheral blood involvement (IV B). In addition, ECP is used in selected cases of early MF when there is peripheral blood involvement (B1). SS can also be treated with MTX at low doses (15–25 mg/week). In patients with disease progression, the recommended therapeutic options include gemcitabine or liposomal doxorubicin. In view of the absence of clinical trials assessing the efficacy of these methods, the recommendations have a level of evidence of IVB. For alemtuzumab, the NCCN level of evidence is IIA [24]. In young individuals, allo-SCT is an option to consider because the prognosis of patients with SS is poor, with a median survival of 2 to 4 years. The main cause of death is infection. Long-term remissions were observed in patients with SS treated with pembrolizumab (phase II clinical trial NCT03385226) who were refractory to treatment/experiencing disease progression after the failure of at least one line of treatment. Out of 15 trial patients, two achieved complete remission (CR), and two – partial remission (PR). In a phase Ib study with nivolumab, an ORR of 15% (in all cases of PR), and SD of 59% were reported. The median PFS was 10 weeks. In a phase I clinical trial with anti-KIR3DL2/CD158, response was achieved in 15 out of 35 patients. A phase II study (TELLOMAK NCT03902184) is currently ongoing [1, 13–18, 28, 29].

It is important to highlight that many of the therapies discussed in European and global recommendations (NCCN and ESMO) are unavailable in Poland due to reimbursement restrictions (fig. 10). Table 9 outlines the therapeutic recommendations in accordance with the Polish reimbursement system. The classic form of MF typically has a chronic clinical course, but achieving a complete cure is rarely possible. In patients with MF stage IA, assessing treatment effects through clinical evaluation is adequate. However, in more advanced disease stages, when lesions resolve leaving skin discoloration, histopathological verification should be considered to determine the degree of lesion resolution [1, 3, 12–17].

Primary cutaneous CD30+ T-cell lymphoproliferative disorders (CD30+ PCTLD)

Primary cutaneous CD30+ T-cell lymphoproliferative disorders represent a spectrum including primary cutaneous anaplastic large cell lymphoma (PC-ALCL), lymphomatoid papulosis (LyP) and 'borderline' cases with overlapping clinical and histopathological features. A key element in establishing the diagnosis of PCTLD is correlating the clinical presentation to the histopathological characteristics; the diagnosis cannot be made solely based on histopathological findings.

Lymphomatoid papulosis (LyP)

Lymphomatoid papulosis is a chronic recurrent skin disorder that presents clinically by papules with mild scale which have a tendency to disintegrate and form superficial ulcers (fig. 11). The papules may resolve spontaneously in 3–12 weeks. LyP primarily occurs in adults, with a slightly higher prevalence

in men. The median age at diagnosis is 45 years. The disorder has a very favorable prognosis, with a 5-year survival rate of 100%, even though complete cure is not possible. Importantly, 20–40% of patients have another coexisting lymphoid malignancy, most commonly cutaneous anaplastic large cell lymphoma (CALCL), MF, Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL). Hence, regular monitoring of LyP patients is essential. The frequency of imaging and blood tests is not preestablished; rather, it should be decided based on the patient's overall condition and any reported subjective symptoms [1, 12–18, 23, 24, 30].

The histopathological features are heterogeneous, with six LyP subtypes identified according to the 2018 WHO-EORTC classification (table 10). The phenotype is similar to that found in cALCL; subtypes D, E, and those with DUSP22 rearrangement express CD8. Various histologic types of LyP can mimic lymphomas with a far more aggressive course. In such cases, the correlation of the clinicopathological features becomes crucial for an accurate diagnosis. The staging system for LyP is shown in table 4. In typical cases, imaging evaluation is not performed to determine the TNM stage (because the disease does not normally affect visceral organs) but to rule out coexisting lymphoproliferative disorders.

Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)

Primary cutaneous anaplastic large cell lymphoma occurs most commonly in adult men. Clinically, it

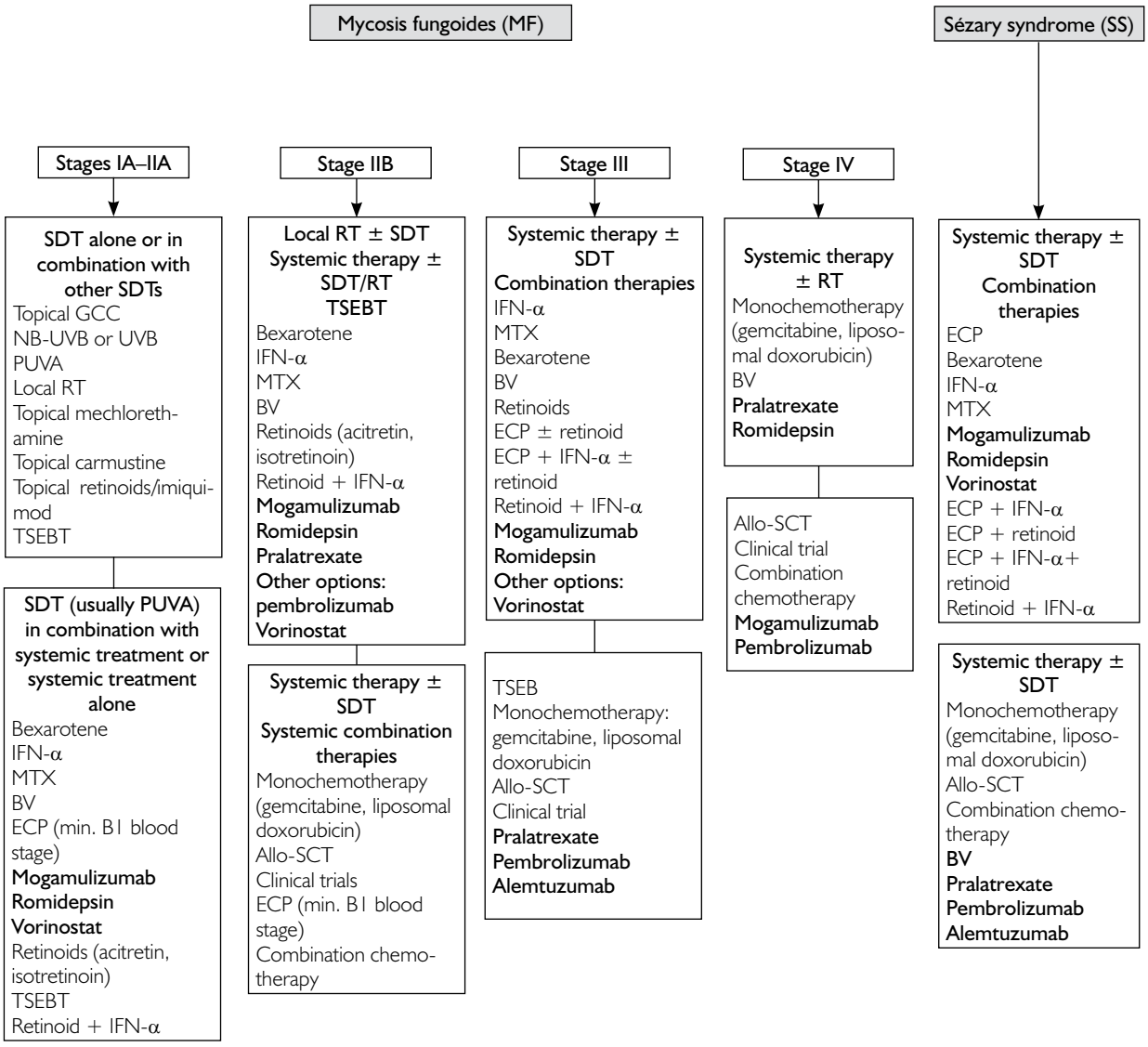

Figure 10. Recommendations for the treatment of MF/SS in accordance with the ESMO 2018 and NCCN 2023 Guidelines

BV – brentuximab vedotin, ECP – extracorporeal photopheresis, IFN-α – interferon α, MTX – methotrexate, TSEBT – total skin electron beam therapy, drug names in bold – no reimbursement in Poland.

Table 9. Recommendations for the treatment of MF, MF-LCT, and SS in the Polish therapy reimbursement system (based on the 2018 ESMO and 2023 NCCN Guidelines)

Skin-directed therapy (SDT)	
Limited/localized skin lesions	**Generalized skin lesions**
Radiation therapy to affected skin area (20–24 Gy) Phototherapy • UVB or narrowband UVB (NB-UVB) Topical glucocorticosteroids Topical imiquimod (off-label) Topical mechlorethamine (RDTL) Topical retinoids (off-label) Topical carmustine (category **IIB**) Useful under certain circumstances: Topical calcineurin inhibitors (pimecrolimus)	Phototherapy • UVB or NB-UVB • PUVA, UVA1 Topical glucocorticosteroids Topical mechlorethamine (RDTL) Total skin electron beam therapy (TSEBT) (12–36 Gy)
Treatment regimens according to disease stage	
MF stages IA–IIA	
First line: skin-directed therapy (SDT) alone or in combination with other SDTs	**Second line:** SDT (usually PUVA) + systemic therapy
Ultra-high-potency topical glucocorticosteroids NB-UVB (for patches) PUVA (for generalized lesions or plaques) Topical mechlorethamine (under RDTL) Topical imiquimod (off-label) Topical retinoids (off-label) Local RT TSEBT (for generalized lesions)	Bexarotene (according to the drug program) Retinoids: acitretin, isotretinoin IFN-α Methotrexate Brentuximab vedotin (when CD30+; according to the drug program) TSEBT Clinical trial **Useful under certain circumstances:** ECP (not widely available; reserved for patients with stage IA/IB/IIA disease with peripheral blood involvement (B1))
MF stage IIB	
First line: local RT alone ± other SDTs (most commonly PUVA); Systemic therapy ± SDT Systemic therapy ± RT TSEBT (for generalized lesions)	**Second line:** systemic therapy ± SDT or combination therapies
Local RT alone ± SDT **Retinoids (acitretin, isotretinoin)** IFN-α Methotrexate Bexarotene (according to the drug program) Brentuximab vedotin (when CD30+; according to the drug program) Retinoid + IFN-α	Monochemotherapy: gemcitabine, liposomal doxorubicin Allo-SCT (allogeneic hematopoietic cell transplantation) – where indicated, e.g. in patients refractory to previous therapies Clinical trial Combination chemotherapy **Useful under certain circumstances:** ECP (currently not widely accessible; recommended for B1 or B2)
MF stage III	
First line: systemic therapy + SDT (most commonly PUVA)	**Second line:**
Retinoids: acitretin, isotretinoin IFN-α Methotrexate Bexarotene (according to the drug program) ± SDT Brentuximab vedotin (when CD30+; according to the drug program) ECP (currently not widely available) Combination therapies: – ECP + IFN-α or retinoid – ECP + IFN-α + retinoid – Retinoid + IFN-α	TSEBT Monochemotherapy: gemcitabine, liposomal doxorubicin Allo-SCT (allogeneic hematopoietic cell transplantation) – where indicated, e.g. in patients refractory to previous therapies Clinical trial
MF stage IV (excluding SS)	
First line: systemic therapy ± RT (to control the local skin status)	**Second line:**
Monochemotherapy: gemcitabine, liposomal doxorubicin Brentuximab vedotin (when CD30+; according to the drug program)	Combination chemotherapy (according to the regimen recommended for PTCL-NOS in the NCCN Guidelines) Allo-SCT (allogeneic hematopoietic cell transplantation) – where indicated, e.g. in patients refractory to previous therapies Clinical trial

Tabela 9. Cont.

Treatment regimens according to stage of advancement	
SS (IVA1 or IVA2)	
First line: systemic therapy + SDT	**Second line:** systemic therapy + SDT
Bexarotene (according to the drug program) ECP (currently not widely available) IFN-α Methotrexate Combination therapies: – ECP + IFN-α or retinoid – ECP + IFN-α + retinoid – Retinoid + IFN-α	Monochemotherapy: Gemcitabine, Liposomal doxorubicin Allo-SCT (allogeneic hematopoietic cell transplantation) – where indicated, e.g. in patients refractory to previous therapies Clinical trial Combination chemotherapy
MF-LCT	
TSEBT or systemic therapy + SDT	
Brentuximab vedotin (when CD30+; according to the drug program) Gemcitabine Liposomal doxorubicin Combination chemotherapy (according to the regimen recommended for PTCL-NOS in the NCCN Guidelines) Allo-SCT (allogeneic hematopoietic cell transplantation) – where indicated, e.g. in patients refractory to previous therapies	

manifests with solitary (80%) or multiple (20%) nodules or tumors, 1 to 10 cm in diameter (TNM staging system – table 4) (fig. 12). Solitary tumors undergo spontaneous involution in one-third of cases. Once remission is achieved, no further treatment is necessary. About 10% of patients may experience secondary involvement of the adjacent lymph nodes. In such cases, secondary skin involvement by systemic ALCL, HL or MF CD30+ should be ruled out.

To establish the diagnosis of PC-ALCL, the clinical and histopathological features must be correlated. Histopathological examination of the skin shows a diffuse infiltrate of CD4+ cells with loss of CD2, CD3 and/or CD5 expression. In CALCL, 75% of infiltrating cells are CD30+. Cancer cells express CLA, with no EMA (epithelial membrane antigen) and ALK expression. Genetic alterations include TCR rearrangement, typically the absence of ALK rearrangement, and the presence of DUSP22-IRF4 rearrangement at locus 6p25.3, which is observed in 25% of cases. The prognosis in PC-ALCL is good, with a 5-year survival rate of 93% in stages T1 and T2, and 77% stage T3. Patients with extensive limb disease (ELD) generally have a poorer prognosis.

Treatment of primary cutaneous CD30+ T-cell lymphoproliferative disorders

Given the indolent, recurrent nature of LyP, the condition does not require treatment. Therapy usually does not impact the prognosis; its purpose is to alleviate symptoms in affected patients. As per the NCCN guidelines, besides the 'wait-and-see' approach, patients with limited skin lesions but with accompanying symptoms may be treated with topical glucocorticosteroids or phototherapy, with a preference for NB-UVB over PUVA. If skin lesions are severe or located in UV-exposed areas, such as the hands and face, clinical improvement is achieved by administering methotrexate (MTX) at a dose of 10–35 mg once a week, along with folic acid supplementation of 5 mg once a week on the day following MTX administration. Other available therapies include PUVA, re-PUVA (PUVA combined with retinoids or rexinoids), and PUVA in combination with PEG-IFN-α. Isolated refractory lesions, usually with diameters exceeding 2 cm, can be removed surgically or treated

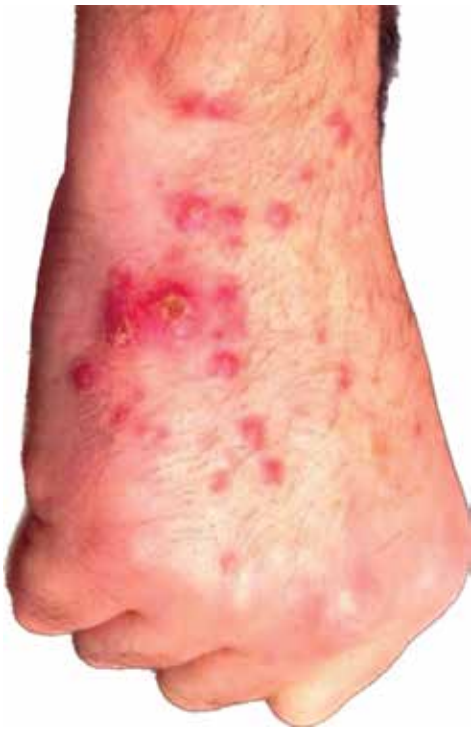

Figure 11. Disintegration and formation of superficial ulcers in lymphomatoid papulosis

Table 10. Histopathological types of LyP and differential diagnosis depending on histopathological features

Histologic types of LyP	Differential diagnosis
A (most common, > 80%) Diffuse or small infiltrates of large atypical CD30+ cells, with the presence of inflammatory infiltration of neutrophils, eosinophils, histiocytes, and small lymphocytes predominant immunophenotype: CD4+, CD8–	pc-ALCL MF tumor stage Hodgkin's lymphoma
B (< 5%) Epidermotropism with infiltration of small and medium-sized atypical lymphocytes Predominant immunophenotype: CD4+, CD8–	MF plaque stage
C (10%) Dense monomorphic infiltrate of large atypical CD30+ cells, relatively few inflammatory cells Predominant immunophenotype: CD4+, CD8–	pc-ALCL MF with CD30+ large cell transformation Adult T-cell leukemia/lymphoma
D (< 5%) Marked epidermotropism of atypical lymphocytes with hyperchromatic nuclei and scanty cytoplasm, and CD8 and CD30 expression Predominant immunophenotype: CD4–, CD8+	Primary cutaneous aggressive Epidermotropic CD8+ T-cell lymphoma Pagetoid reticulosis
E (< 5%) Angioinvasive and angiodestructive infiltrates of atypical small and medium-sized CD30+ cells; necrosis, hemorrhage, and ulceration Predominant immunophenotype: CD4–, CD8+	Extranodal NK/T-cell lymphoma, nasal type Primary cutaneous gamma-delta T-cell lymphoma
With DUSP22-IRF4 rearrangement (< 5%) Predominant immunophenotype: CD4-, CD8+ or CD4-, CD8-	MF with CD30+ large cell transformation

with radiation therapy. Patients with CD30+ lymphoproliferative disorders not responding to topical therapies or MTX may be treated with BV. However, this modality is recommended only in the NCCN guidelines and it is not included in the 2018 ESMO guidelines. Similarly, in Poland, BV is not listed in the drug program B.66.

The choice of PC-ALCL therapy depends on the clinical manifestation. Solitary tumors can be treated surgically or with radiation therapy at a dose of 24–50 Gy, most commonly 24–30 Gy (2 Gy fraction), with a 2 –3 cm safety margin of non-tumorous tissue around the tumor. A complete remission is achieved in 95% of cases. Other therapeutic options to consider include MTX at a dose of up to 30 mg per week, PEG-IFN-α, or bexarotene (however, the drug program in Poland does not provide for this indication). Upon remission of the disease, treatment can be gradually discontinued, typically with no relapse. For patients with no response/with relapse after one systemic therapy, brentuximab vedotin (BV) at a dose of 1.8 mg/kg *i.v.* every 3 weeks should be considered. The dose must be adjusted according to the CHPL, for example, in case of renal or hepatic impairment. In line with the 2023 NCCN guidelines, BV is the preferred treatment for multifocal lesions. Other recommended regimens include MTX, retinoids, pralatrexate, and PEG-IFN-α, either alone or in combination with skin directed therapy (SDT). PC-ALCL with lymph node involvement, after ruling out systemic ALCL, can be treated with BV in combination with local RT and other BV regimens with polychemotherapy (CHP: cyclophosphamide, doxorubicin, prednisone), MTX ± local RT, pralatrexate ± local RT, CHOP or CHOEP ± local RT in eligible cases. Polychemotherapy is considered as a treatment of last resort, particularly in patients with visceral organ involvement and when there has been no response to prior therapies [1, 12–16, 18, 22, 30]. A summary of therapeutic recommendations in PCTLD is shown in table 11.

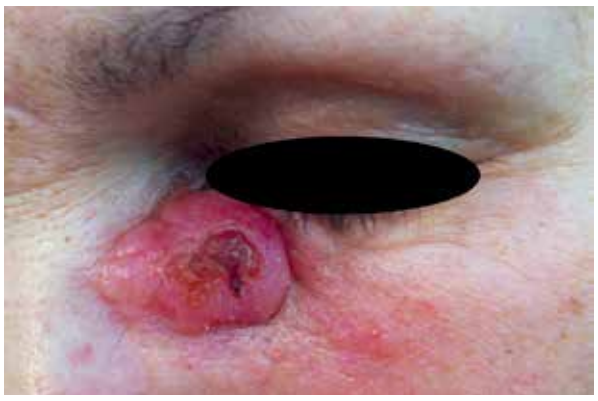

Figure 12. Solitary tumor in primary cutaneous anaplastic large-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

Subcutaneous panniculitis-like T-cell lymphoma is a rare tumor that affects both adults and children, occurring with equal frequency in both sexes. It presents as a solitary tumor or multiple tumors and/or infiltrates manifesting as subcutaneous panniculitis, located on the extremities and trunk. The skin lesions

Table 11. Treatment of PCTLD based on the Polish reimbursement system according to the ESMO 2018 and NCCN 2023 Guidelines

LyP	
First line	**Second line**
Watchful waiting (preferred approach) Topical glucocorticosteroids	MTX Phototherapy (NB-UVB, PUVA) Diffuse LyP: Systemic retinoids (limited data) Topical mechlorethamine
PC-ALCL	
Solitary or grouped nodules:	
Local radiation therapy Surgical excision	
Multifocal lesions:	
First line	**Second line**
MTX RT	Brentuximab vedotin (when CD30+; according to the drug program) Other regimens ± SDT: Retinoids (limited data) IFN-α Watchful waiting when asymptomatic

are commonly accompanied by elevated body temperature, fatigue, body weight loss, peripheral blood cytopenia, and increased blood transaminase levels. SPTCL can be complicated by hemophagocytic syndrome (HPS). The prognosis is more favorable for patients without HPS, with 91% surviving 5 years, compared to 46% for those with HPS.

Histopathological examination reveals infiltration of lymphoma cells with the immunophenotype ab (CD3+, CD4–, CD5–, CD7+, CD8+, CD56–, CGP+), confined to the subcutaneous tissue, without dermal and epidermal involvement.

The recommended treatment is based on systemic glucocorticosteroids (prednisone 30–50 mg/day); in refractory cases, they may be combined with low doses of MTX or bexarotene or cyclosporine. However, this method is controversial due to its known pro-lymphoproliferative effect (cyclosporine can induce or contribute to the progression of lymphoproliferative processes). For HPS, it may be necessary to employ the treatment strategy used in aggressive mature T-cell lymphomas: chemotherapy (CHOP) and/or radiation therapy (up to 40 Gy). Patients with CHOP-refractory HPS can be treated with cladribine, DHAP, ESHAP, FLAG, mini-BEAM, and allo-HSCT [1, 13–18, 22].

Ultra-rare cutaneous T-cell lymphomas

In the absence of clinical trials and studies involving large patient groups, diagnostic and therapeutic suggestions are not considered formal recommendations. Treatment decisions should be based on the evaluation of the clinical course and lymphoma subtype. Lymphomas with a favorable prognosis are typically managed with local treatments, surgery or radiation therapy, while aggressive variants are treated systemically, following a similar approach as in other T-cell lymphoma types.

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSMP-TLPD)

PCSMP-TLPD is a type of indolent lymphoma. Clinically, it presents as solitary infiltrates or nodules, typically located on the skin of the face/neck, and upper trunk. The diagnosis may only be established when typical MF lesions are absent (also in the patient's medical history). The disorder has a very favorable prognosis, with a 100% 5-year survival rate.

Histopathological examination of the skin reveals a dense diffuse infiltrate containing small and medium-sized T cells with CD3+, CD4+, CD8– and CD30– phenotypes, and a significant proportion of B cells and histiocytes. Large pleomorphic T-cells account for < 30% of cells. The tumor infiltrate penetrates into the deeper layers of the dermis and subcutaneous tissue; focal epidermotropism may be present. Given that the disease does not affect visceral organs, imaging assessment is not necessary.

Therapeutic options include surgical excision, local radiation therapy, or intralesional steroid treatment [13–15, 18, 31]. In some cases, skin lesions resolve spontaneously after biopsy, with no need for treatment.

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL)

AECTCL is clinically characterized by the presence of localized or diffuse papules, nodules, and

tumors, often with central necrosis. Lymphoma infiltrates can also be detected in the lungs, testicles, central nervous system (CNS), and oral mucosa, although lymph nodes are not typically enlarged. The median survival is 32 months [13–15, 17, 25, 32, 33]. The prognosis is unfavorable, with a 5-year survival rate of 31–32% [32, 33].

Histopathological examination of the tumor infiltrate reveals the presence of epidermotropic T cells with the phenotype of CD3+, CD8+, bF1+, granzyme B+, perforin+, TIA-1+, CD45RA+, CD45RO–, CD2–, CD4–, CD5–, CD7+/–. AECTCL should be differentiated from indolent primary cutaneous acral CD8+ T-cell lymphoma (tumor lesions in the ear and nose), which is characterized by similar histopathology and phenotype. The clinical course of AECTCL is aggressive, with TNM-based evaluation required.

Most centers follow a treatment strategy based on multidrug chemotherapy in combination with radiation therapy. Young individuals and patients in a good general condition should be considered for allo-HSCT (recommendation based on evidence level IVB).

Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL)

PCGD-TCL presents clinically with diffuse plaques and/or papules as well as superficially ulcerating nodules, located mainly on the extremities. Mucous membranes and other extranodal locations are frequently involved (in 50% of cases), but lymph node, spleen, or bone marrow involvement is rare. The clinical course is highly aggressive. The stage of disease should be determined according to the Ann Arbor system. The prognosis is unfavorable, with a 5-year survival rate of 11% [32, 33] and a median survival of 15 months [13–16, 18, 32, 33].

Histopathological examination of the skin reveals T cell infiltrates with the following phenotype: CD2+, CD3+, CD5+, CD7+/–, CD56+, bF1–, γ/δ+ and CD4– and CD8–, which can be found in the epidermis, dermis or subcutaneous tissue.

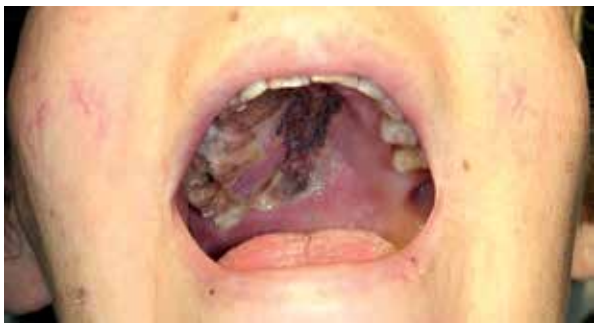

Figure 13. Nasopharyngeal infiltrations with destruction of surrounding tissue in extranodal nasal-type NK/T-cell lymphoma

Optimal treatment is currently unknown. Most centers follow a treatment strategy based on multidrug chemotherapy in combination with radiation therapy applied to isolated lesions (24–30 Gy). Clinical trials have explored treatments such as ruxolitinib, cerdulatinib, and duvelisib (NCT02974647, NCT01994382, NCT02783625). Young patients in a good general condition should be considered for allo-HSCT (recommendation based on evidence level IVB).

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL)

ENKTCL is a rare lymphoma with an aggressive course, associated with Epstein-Barr virus (EBV) infection. It is characterized by multiple patches or tumors located on the skin of the trunk and extremities – or a solitary tumor in the nasopharynx with a tendency to destroy surrounding tissues (fig. 13). The skin is the second most frequent extranodal site for ENKTCL. Histopathological examination reveals NK/T-cell infiltrates within the dermis and in the subcutaneous tissue, occasionally with epidermotropism. The 5-year overall survival ranges from 38% to 55% [32, 33]. Patients with lesions limited solely to the skin have a better prognosis, with a median survival of 27 months. In patients with extracutaneous lesions, the median survival is 5 months [32, 33].

In patients with limited disease (Ann Arbor stages I–II), the treatment of choice is sequential therapy: chemotherapy followed by consolidation radiation therapy or concurrent chemotherapy and radiation therapy. Advanced ENKTCL (Ann Arbor stages III–IV) and relapses are treated with chemotherapy including regimens based on L-asparaginase and etoposide [33].

Primary cutaneous acral CD8+ T-cell lymphoma (acral CD8+ TCL)

Primary cutaneous acral CD8+ T-cell lymphoma follows an indolent course, with involved sites including the feet, hands, auricles, or nose. Clinically, it presents as a slow-growing papule or nodule in a solitary location.

Histopathologically, a diffuse monomorphic infiltrate of small to medium-sized T cells is found in the skin, less commonly in subcutaneous tissue, showing the immunophenotype of CD3+ CD8+ βF1+ CD4- CD30- CD56- CD20-. TCR rearrangement is usually monoclonal. Imaging assessment is not necessary, as the disease does not spread to the visceral organs.

Available therapies include topical or intralesional glucocorticoids, surgical resection, and radiation therapy [16, 31–33]. The 5-year survival rate is 100% [32, 33].

PRIMARY CUTANEOUS B-CELL LYMPHOMA (PCBCL)

In the 2005 WHO-EORTC classification, three main types of CBCL were identified: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT). However, PCFCL and PCDLBCL, LT, were described as separate entities in the 2008 WHO classification and in its 2016 revision. Meanwhile, PCMZL was included in the group of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT), despite differences in histologic features, genetic profile, and clinical course. EBV+ mucocutaneous ulcer was listed as a new provisional entity in the 2017 revision of the WHO classification and in the updated 2018 WHO-EORTC classification [34]. The characteristics of the three most common CBCL types are summarized in table 12.

Primary cutaneous marginal zone lymphoma (PCMZL)

Primary cutaneous marginal zone lymphoma is a type of lymphoma with an indolent clinical course. PCMZL commonly involves the mucosa, and it is classified in the group of MALT (mucosa-associated lymphoid tissue) lymphomas [1].

PCMZL accounts for 7% of all primary cutaneous B-cell lymphomas and is the second most prevalent type of PCBCL after PCFCL. The condition usually affects middle-aged individuals, with the median age at diagnosis in the third to sixth decades of life. PCMZL is more prevalent in men compared to women.

Clinically, it is characterized by skin eruptions consisting of papules, plaques, or nodules that range in color from red to violaceous. The lesions are typically located on the trunk and arms, less commonly on the lower extremities (fig. 15 A, dermoscopic diagnosis). They are typically multifocal, with solitary lesions found only in a minority of cases. A small number of patients experience generalized symptoms. A distinctive feature of PCMZL is the recurrence of skin lesions, particularly in patients with multifocal disease. Extracutaneous dissemination is rarely observed.

PCMZL is characterized by a very indolent clinical course and an excellent prognosis, with a 5-year survival rate close to 100%, depending on the subtype. In some cases, spontaneous resolution of skin lesions is observed, accompanied by the development of secondary anetoderma resulting from the loss of elastic fibers in the region of tumor infiltration. In some European patients, an association has been found between the development of PCMZL and *Borrelia burgdorferi* infection [1, 35].

Table 12. Differentiation of the most common CBCL subtypes

Parameter	Primary cutaneous marginal zone lymphoma (PCMZL)	Primary cutaneous follicle center lymphoma (PCFCL)	Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT)
Symptoms	Mean age of onset: approximately 55 years Solitary or multiple papules or nodules located most commonly on the extremities; reported link with *Borrelia burgdorferi* infection	Mean age of onset: 50 years; same prevalence in men and women Solitary or grouped multiple tumors located usually on the head or trunk	Mean age of onset: 76 years, predilection for women Solitary or grouped multiple tumors located usually on the lower extremities, less commonly in other sites
Histopathological features	Dermal infiltrate of small B cells, including centrocytes, lymphoplasmacytoids, and plasma cells; with epidermal sparing	Papular and/or diffuse infiltrate composed mainly of centrocytes and centroblasts	Diffuse infiltrate of centroblasts and immunoblasts
Phenotype	CD20+, CD79a+, Bcl-2+, CD5–, Bcl-6 -, CD10–, MUM-1- Possible IgH/MALT-1 translocation	CD20+, CD79a+, Bcl-6+, Bcl-2–, MUM-1–, CD5-, CD10 -, FOXP1-(±)	CD20+, CD79a+, Bcl-6+/–, CD10–, CD5-, Bcl-2+, MUM-1+, FOXP1+ CDKN2A deletion, IgH/MYC translocation, blc2 and MALT1 amplification, MUD88 mutation
Staging	CBC with differential, LDH, serum protein electrophoresis, neck-to-pelvis CT, lymph node ultrasound	CBC with differential, LDH, serum protein electrophoresis, neck-to-pelvis CT, lymph node ultrasound, bone marrow biopsy	CBC with differential, LDH, serum protein electrophoresis, neck-to-pelvis CT, lymph node ultrasound, bone marrow biopsy, esophagogastroduodenoscopy
Prognosis	Frequent relapses without worsening prognosis, 5-year survival rate > 95%	Frequent relapses without worsening prognosis, 5-year survival rate > 95%, but in patients with leg involvement: 40%, in patients with visceral involvement: 5–10%	5-year survival rate 60%; negative prognostic factors: multiple lesions, MYD88 mutation, IgH/MYC translocation

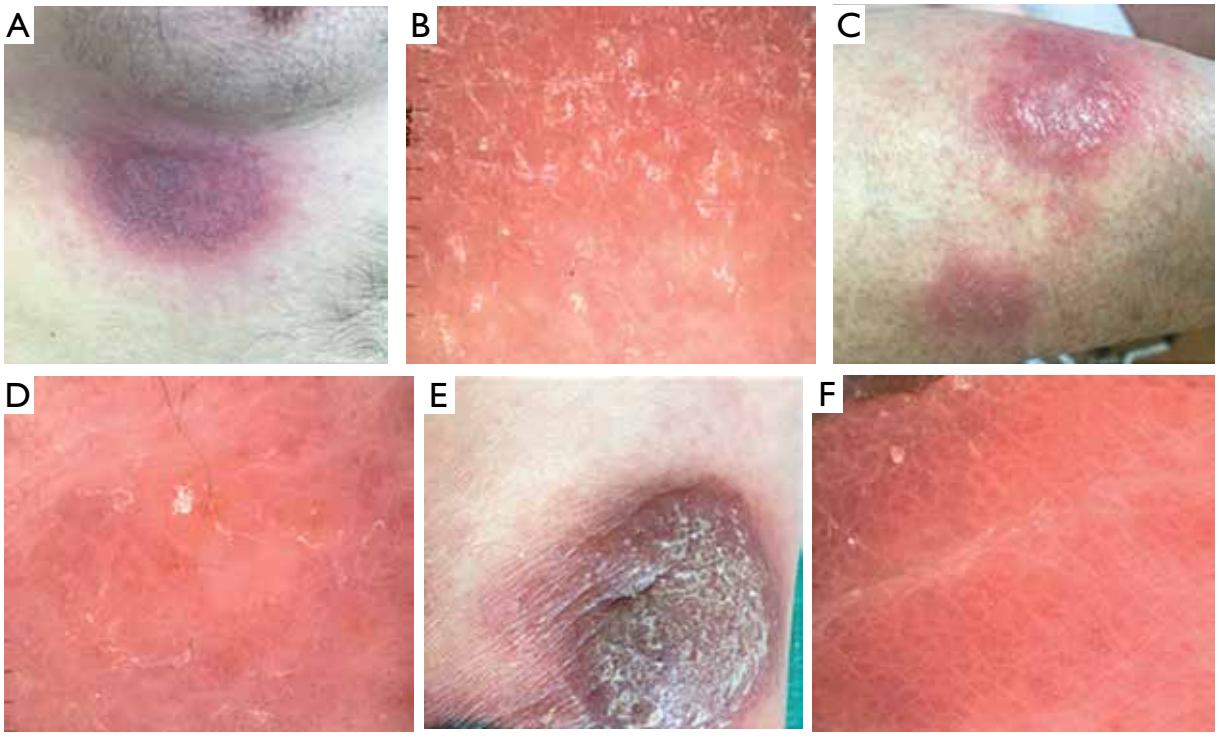

Figure 14. A – Mycosis fungoides (MF) presenting clinically as a solitary patch (patch stage, IA). **B** – Polarized-light dermoscopy image of MF patch stage revealing white scale and linear-curved vessels. **C** – Clinical characteristics of MF patch stage (IB). **D** – Polarized-light dermoscopy image of focal MF plaque revealing grouped arrangement of dotted vessels. **E** – Clinical characteristics of MF tumor stage (IIB). **F** – Polarized-light dermoscopy image of MF tumor revealing red globules separated by white lines

On histopathological examination, PCMZL shows nodular or diffuse infiltration with epidermal sparing. Infiltrates are composed of small lymphocytes, marginal zone (centrocyte-like) B cells, lymphoplasmacytoid cells, and plasmacytes. Additionally, there are small amounts of centroblast-like or immunoblast-like cells, along with numerous reactive T cells. Reactive germinal centers are frequently observed, which may be surrounded by a population of small or medium-sized cells.

On immunophenotypic assessment, marginal zone B cells express CD20, CD79a, and Bcl-2, and are negative for CD5, CD10, and Bcl-6. Plasmacytes show the presence of CD138 and CD79a markers, as well as monotypic expression of cytoplasmic immunoglobulin light chain on paraffin sections.

Primary cutaneous follicle center lymphoma (PCFCL)

Primary cutaneous follicle center lymphoma is defined as a neoplastic proliferation of germinal center cells confined to the skin. Clinical presentation includes solitary or grouped papules, plaques, or nodules, pink in color, usually with a red border (fig. 15 C, dermoscopic diagnosis). Less commonly, disintegration and ulcer formation are observed on the surface of the lesions. PCFCL typically involves the skin of the head, especially the forehead, and the trunk, particularly the back. The condition usually does not cause any clinical symptoms. Serum LDH levels are typically within the limits of norm. The prognosis is favorable. Although relapses occur in approximately 50% of patients, dissemination to lymph nodes or visceral organs is rarely observed.

Histopathological examination of PCFCL shows nodular or diffuse infiltrates across the entire width of the dermis, often extending into the subcutaneous fat tissue. The epidermis is usually lesion-free. A distinct follicular pattern with the formation of neoplastic germinal centers has been observed in only a minority of cases (25%). More commonly, only some elements of the follicular pattern are identified. In patients with the follicular pattern, the neoplastic follicles show characteristic morphological features of malignancy. The phenotype is CD20+, CD10-, BCL6+, BCL2–, MUM1–, FOXP1–.

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT)

PCDLBCL-LT is an aggressive type of CBCL, characterized by the proliferation of centroblasts and/or immunoblasts. It occurs almost exclusively in elderly individuals, predominantly women. In contrast to PCFCL, PCDLBCL-LT lesions more commonly spread to extracutaneous sites, and the condition carries a less favorable prognosis. Clinically, patients present with a solitary fast-growing tumor or a group of tumors, pink-red or red-brown in color. Lesions are

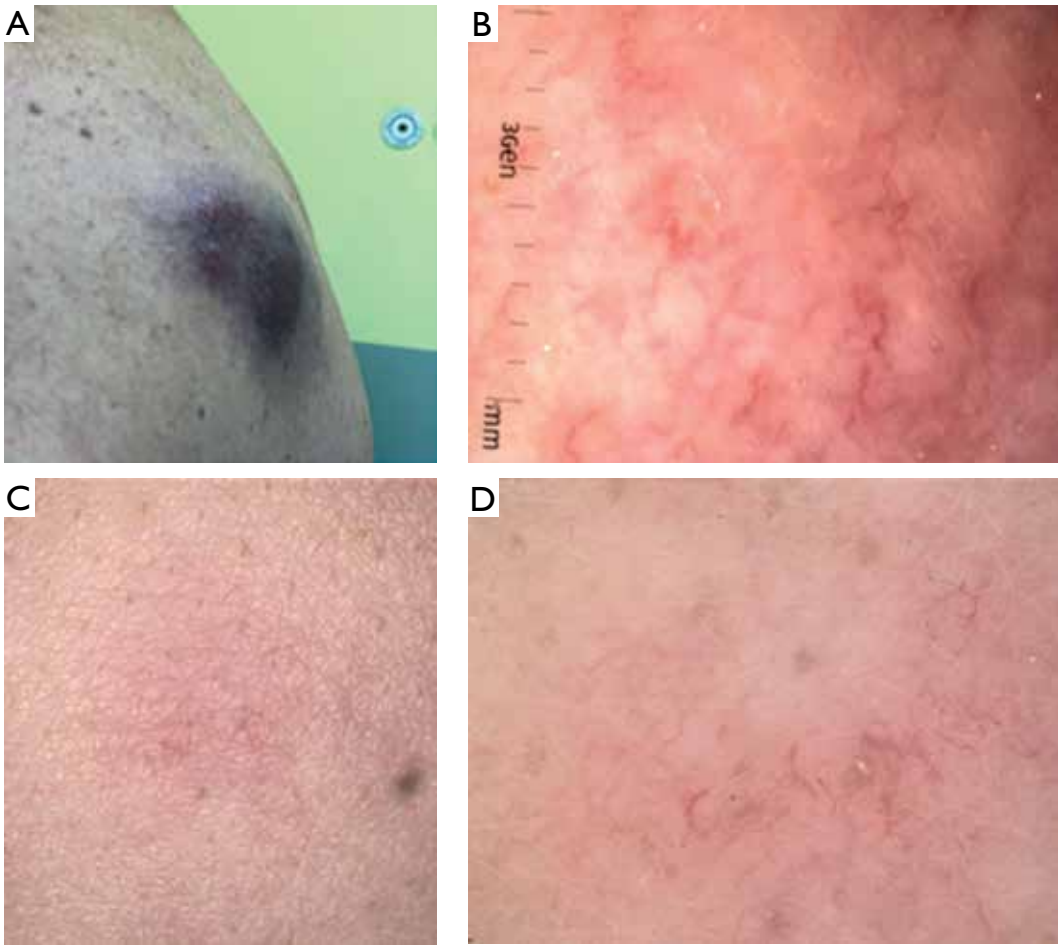

Figure 15. A – Clinical characteristics of tumor lesion in primary cutaneous marginal zone B-cell lymphoma (PCMZL). **B** – Polarized-light dermoscopy image dominated by irregular serpentine vessels and branching linear vessels. **C** – Clinical characteristics of plaque lesion in primary cutaneous follicle center lymphoma (PCFCL). **D** – Polarized-light dermoscopy image revealing fine short linear vessels

located predominantly on the distal lower extremity. In some patients, tumors may develop on both lower extremities concurrently. In other cases, shortly after appearing on one leg, another tumor develops on the other leg. The tumor surface may become ulcerated. Small erythematous papules may occasionally appear in the proximity of larger tumors. In around 20% of cases, tumors exhibiting similar morphological and phenotypic characteristics may develop in locations other than the lower extremities [36, 37]. The prognosis in DLBCL-LT is less favorable than in other types of PCBCL, with a 5-year survival rate of approximately 50%.

Histopathologically, the condition presents with a diffuse lymphoid infiltrate, primarily composed of immunoblasts and centroblasts, observed throughout the dermis and subcutaneous tissue, extending to the dermal-epidermal border. Reactive small lymphocytes are either scarce or absent, with high mitotic activity. The immunophenotype of tumor cells is characterized by the expression of monoclonal surface immunoglobulins and/or cytoplasmic immunoglobulins. B cell markers (CD20, CD79a), as well as MUM1 and FOX-P1, are present. In all patients with primary cutaneous DLBCL-LT, Bcl-2 expression is observed. In rare cases of typical cutaneous DLBCL-LT, tumor cells are CD30 positive [38, 39]. Whole-body PET-CT scan is recommended in the diagnostic process.

Patients with PCMZ presenting as solitary or multiple lesions can be treated with radiation therapy (24–30 Gy) or surgical resection. According to the NCCN recommendations, in addition to the above therapies, SDT and intralesional glucocorticosteroids may be considered for treatment. In selected patients, watchful waiting may be recommended. In patients with concomitant *Borrelia burgdorferi* infection, targeted systemic antibiotic therapy should be initiated. In patients with multifocal skin lesions, approximately 50% may achieve a complete response with the administration of chlorambucil or interferon α. Very good outcomes have also been reported for treatment with systemic or intralesional anti-CD20 antibody (rituximab). In hospitalized patients experiencing frequent recurrences of skin lesions, topical or intralesional steroid therapy may be considered. In asymp-

tomatic individuals, treatment may be deferred until disease progression has been documented [40, 41].

The recommended therapeutic option in patients with PCFCL presenting with solitary lesions is radiation therapy (24–30 Gy). It is a safe treatment method, and highly effective, with a total remission rate close to 100%. Complete resection of the lesion is another potential approach, which can delay radiation therapy until disease relapse. While radiation therapy is typically advised for patients with a single lesion, radiation therapy or watchful waiting is recommended for individuals with multiple lesions [41]. In patients with extensive skin involvement, rituximab monotherapy is the treatment of choice. In approximately one-third of patients, relapse may occur following radiation therapy or rituximab treatment. However, since such relapses usually remain confined to the skin, they can be managed similarly to the initial therapy prescribed for the treatment of PCFCL [42, 43].

Cutaneous PCDLBCL-LT has a similar clinical course to systemic DLBCL. Patients are treated with immunochemotherapy (R-CHOP regimen: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). The efficacy of this treatment in PCDLBCL-LT and in high-risk systemic DLBCL is similar [41]. R-CHOP with adjuvant local radiation therapy (36–40 Gy) is also recommended, or radiation therapy alone (40 Gy) – in patients who are ineligible for chemotherapy. When a patient is not eligible for polychemotherapy and radiotherapy, treatment with rituximab monotherapy can be considered [44]. New drugs used in the treatment of PCDLBCL-LT include dacetuzumab (anti-CD40 antibody), immune checkpoint inhibitors (anti-PD1 and anti-PD-L1), and Bruton's tyrosine kinase inhibitor [45]. Also, encouraging results from a phase II clinical trial involving intralesional administration of genetically modified viruses (IFN-γ adenovirus, TG1042) have been reported. A phase I trial evaluating treatment with intralesionally administered T-VEC (talimogene laherparepvec), a genetically modified HSV-1 known for its good response in melanoma, is ongoing. Cases of successful treatment of CBCL with photodynamic therapy (5-ALA and red light) have been reported as well. Another available therapeutic option for patients with PCLBCL-LT is lenalidomide (CR and PR in 4 and 8 out of 19 patients, respectively) [1, 12–16, 34, 35, 41, 46, 47]. Recommended treatment strategies for CBLC are outlined in table 13.

Primary cutaneous diffuse large B-cell lymphoma, not otherwise specified (PCDLBCL–NOS)

The term PCDLBCL-NOS was introduced in the WHO-EORTC classification in 2005 to cover rare cases of DLBCL with a primary cutaneous location that do not fit the criteria for classification as PCDLBCL-LT or PCFCL. However, the term was interpreted in various ways and caused considerable confusion. To resolve this issue, the WHO-EORTC classification was revised in 2018, with the term PCDLBCL not otherwise specified replaced with DLBCL-NOS.

Intravascular large B-cell lymphoma

Intravascular large B-cell lymphoma is an uncommon condition characterized by the infiltration of blood vessels by large neoplastic B cells. This type of lymphoma commonly affects the central nervous system, lungs, and skin, and is associated with a poor prognosis. A primary cutaneous form has also been reported, where the disease is confined solely to the skin at diagnosis.

Clinically, this lymphoma manifests on the skin as violaceous patches and plaques or telangiectatic lesions, typically found on the lower limbs or trunk. Patients with isolated skin lesions have a more favorable prognosis compared to those with involvement of other sites. The 3-year survival rate is 56% and 22% for patients with the cutaneous and extracutaneous forms, respectively. There are reports where this type of lymphoma manifested on the skin as cherry angiomas. They were infiltrated by tumor

Table 13. CBCL treatment in the Polish therapy reimbursement system

Primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous marginal zone lymphoma (PCMZL)	
Isolated/limited skin lesions	**Disseminated lesions**
Local radiation therapy (preferred approach)	Observation
In selected cases:	SDT – topical or intralesional glucocorticosteroids
Surgical excision of solitary lesion	Local radiotherapy
Antibiotic therapy – for PCMZL and confirmed *Borrelia burgdorferi* infection	**Intralesional rituximab**
	IFN-α
	Chemotherapy (chlorambucil or R-COP or R-CHOP) in patients with diffuse cutaneous lesions or visceral involvement
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-leg type)	
Immunochemotherapy: R-CHOP with local radiation therapy	
Local radiation therapy in chemotherapy-ineligible patients	

cells, representing the sole indication of intravascular large B-cell lymphoma. Histologically, blood vessels in the dermis and subcutaneous tissue are filled with and often dilated by the proliferation of large neoplastic B cells. These cells have the potential to cause occlusion of small venous and arterial vessels as well as capillaries. In some cases, a small number of tumor cells can also be seen around blood vessels [1]. The preferred treatment approach is combined chemotherapy, also in patients with cutaneous manifestations [43].

EBV-positive mucocutaneous ulcers (EBVMCU) and other cutaneous B-lymphocyte lymphoproliferative disorders linked to immunodeficiency

EBV-positive mucocutaneous ulcers occur predominantly in elderly individuals or in patients after immunosuppressive therapy (methotrexate, azathioprine, cyclosporine, anti-TNF treatment).

Clinically, EBVMCU usually manifests as a solitary, sharply demarcated ulcer located on the skin or oropharyngeal or gastrointestinal mucosa. The clinical course is indolent and usually confined to the skin or mucosal sites.

Histologically, the infiltrate is composed of large EBV-positive Hodgkin's B-cells that are interspersed among other cells constituting the inflammatory background. The immunophenotype consists of transformed PAX5+ cells showing variable CD20 expression, non-germinal center phenotype (IRF4/MUM1+, CD10–, BCL6–), and EBV expression. Usually, the cells express CD30, and in half of the cases they also co-express CD15 [1].

DIAGNOSTIC DERMOSCOPY

Dermoscopy (epiluminescence microscopy) is a non-invasive technique used for *in vivo* evaluation of skin lesions. It offers magnifications ranging from 10× with handheld dermoscopes to up to 200× with video dermoscopes. Dermoscopy allows the identification of dermoscopic features that serve as predictors of primary cutaneous T- and B-cell lymphomas (vs. non-invasive inflammatory dermatoses), including orange structureless areas and white lines (vs. pseudolymphomas) [46].

In addition, typical dermoscopic features of selected morphological stages of mycosis fungoides (MF) have been identified. Specific dermoscopic characteristics strongly suggest the subtype of MF, depending on disease stage [48]. The presence of linear and linear-curved vessels with white scale is typical for MF patches (figs. 14 A, B), grouped arrangements of dotted vessels are usually seen in the plaque stage of MF (figs. 14 C, D), while peripheral linear vessels with branching, ulceration, and red globules separated by white lines indicate nodular changes in MF (figs. 14 E, F). Distinctive dermoscopic features associated with various variants of mycosis fungoides facilitate the initial diagnosis of suspected clinical lesions. These include the folliculotropic variant (absence of hair, dilated hair follicle openings, follicular plugs), the erythrodermic variant (linear or dotted vessels, white scaly patches, focal orange structureless areas); and the poikilodermatous variant (focal white and brown structureless areas with white patchy scaling, brown reticular lines).

Knowledge of dermoscopic features can be highly beneficial in the initial differential diagnosis between CTCL and CBCL. The vascular pattern in CTCL reveals unfocused dotted vessels [46], while in the group of cutaneous primary B-cell lymphomas, i.e. in primary cutaneous marginal zone lymphoma (PCMZL) (figs. 15 A, B) and in primary cutaneous follicle center lymphoma (PCFCL) (figs. 15 C, D), dermoscopy usually shows fine, short linear and irregular serpentine vessels against a salmon-colored background [47]. Unfocused linear vessels with branching are indicative of PCMZL (figs. 15 A, B), as opposed to other variants of PCBCL [46]. Diagnostic dermoscopy is also used for monitoring the effects of therapy [49] and determining the optimal location of a skin lesion for obtaining a diagnostic biopsy for histopathological confirmation [48]. Additionally, trichoscopic assessment in erythrodermic MF reveals characteristic findings including pili torti and eight-shaped hairs, thick white interfollicular bands, heterogeneous color of background, and perifollicular vessel distribution [50].

MAIN REIMBURSEMENT EXPECTATIONS BASED ON RELEVANT LITERATURE

Diagnostic and therapeutic recommendations in each country should align with global recommendations.

However, due to the non-reimbursement of certain therapies in the Polish healthcare system – whether in general, for specific cutaneous lymphomas, or particular lines of treatment – adherence to European and global recommendations may be impossible in some patients. There are difficulties with the following therapeutic regimens:

- mechlorethamine – available under emergency access to drug technologies (RDTL);
- bexarotene – under the drug program, bexarotene can be used in the treatment of MF and SS exclusively after two unsuccessful systemic therapies or in patients experiencing toxicity during two treat-

ments; the drug cannot be prescribed, for example, for the treatment of lymphomatoid papulosis;
- brentuximab vedotin – under the drug program, the drug can be prescribed to patients with CD30+ MF at stages up to IIA only after failed systemic therapy (also with bexarotene which, in accordance with the drug program described above, is unavailable, for example, to patients with lymphomatoid papulosis or SS);
- ECP – technically speaking, ECP is available in every transplant center, but because of the lack of reimbursement it cannot be used as set out in global recommendations;
- anti-PD1 and anti-PD-L1 checkpoint inhibitors – no reimbursement available for the treatment of cutaneous lymphomas;
- pegylated liposomal doxorubicin – no reimbursement in SS (in the group of first-line drugs according to the NCCN and ESMO guidelines) and in MF refractory to other treatment modalities (for use in monotherapy or in combination with IFN according to NCCN and ESMO recommendations).

Difficulties also arise because of limited access of dermatologists to PEG-IFN-α. Consequently, patients undergoing treatment with PEG-IFN-α + PUVA must make appointments with a hematologist or oncologist for PEG-IFN-α and separately consult a dermatologist for PUVA therapy. Denileukin diftitox, HDAC inhibitors, alemtuzumab, and mogamulizumab – which are recommended in the ESMO and NCCN guidelines – are not available in Poland.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Received: 23.11.2023
Accepted: 23.02.2024

How to cite this article
Sokołowska-Wojdyło M., Olszewska B., Chmielowska E., Robak E., Prochorec-Sobieszek M., Kamińska-Winciorek G., Maj J., Kowalczyk A., Reich A., Lesiak A., Narbutt J., Szepietowski J., Woźniacka A.J., Owczarczyk-Saczonek A.B., Romejko-Jarosińska J., Giza A., Nowicki R.J., Jaworek A.K., Zaucha J.M.: Primary cutaneous lymphomas. Diagnostic and therapeutic guidelines of the Polish Dermatological Society (PTD) and Polish Lymphoma Research Group (PLRG). Dermatol Rev/Przegl Dermatol 2023, 110, 647–674. DOI: https://doi.org/10.5114/dr.2023.138937.