Management of cutaneous T & B cell lymphomas: a comprehensive review

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SUMMARY

Primary cutaneous lymphomas are a heterogeneous group of diseases with indolent or aggressive behaviour, skin-limited or systemic extension, from T or B cell origin. The optimal management requires the multi-disciplinary approach with dermatologists, hemato-oncologists, pathologists and molecular biologists. The objective of this review is to harmonise the work-up and the treatment of these different entities of cutaneous T or B cell lymphoma in Belgium, according to the availability of the drugs and specialised treatment such as extra-corporeal photopherisis or total skin electron beam therapy.

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INTRODUCTION

Primary cutaneous B (CBCL) and T (CTCL) cell lymphomas constitute a heterogeneous group of non-Hodgkin lymphomas (NHL). After the gastrointestinal tract, the skin is the second most common site of extranodal NHL, with a predominance of T-cell lymphomas (TCL). In 2005, the World Health Organization (WHO) and European Organisation for Research and Treatment of Cancer (EORTC) published a consensus classification for cutaneous lymphomas by distinguishing T and B subtypes.[1] This classification integrated into the 2016 revision of WHO classification of lymphoid neoplasms, gives us the current definition of these neoplasms (*Table 1*).[1,2]

Unlike nodal lymphomas, CTCL are more frequent than CBCL (approximately 75% of TCL), largely due to the relative high incidence of mycosis fungoides.

We have previously described, in the Belgian journal of Haematology, the role of new targeted/immuno-therapies in cutaneous lymphomas. This paper focuses on staging and treatment according to Belgian guidelines, which are based on the latest recommendations issued by the EORTC, the French group of cutaneous lymphomas, the International Society for Cutaneous Lymphoma (ISCL) and the British Association of Dermatology.[3-13] Subcutaneous panniculitis-like T-cell lymphoma (<1% Cut Lymphoma) for which there is no specific therapeutic strategy, will not be discussed in depth.

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TABLE 1. WHO-EORTC Classification of cutaneous T- and B-cell lymphomas.[1,2]

Cutaneous T-cell Lymphoma
Mycosis fungoides (MF)
MF variants and subtypes:
• Folliculotropic MF
• Pagetoid reticulosis
• Granulomatous slack skin
Sézary syndrome (SS)
Adult T-cell leukaemia/lymphoma (ATLL)
Primary cutaneous CD30-positive lymphoproliferative disorders:
• Primary cutaneous anaplastic large cell lymphoma
• Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal-type
Hydroa vacciniforme-like lymphoproliferative disease
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous γ/δ T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, unspecified
Cutaneous B-cell Lymphoma
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle centre lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
EBV+ mucocutaneous ulcer
Primary cutaneous diffuse large B-cell lymphoma, other
Primary cutaneous intravascular large B-cell lymphoma

Patients with cutaneous lymphoma consult both dermatologists and haematologists. A close collaboration between both specialisms is necessary at the moment of diagnosis and during the follow-up of the patient in order to propose, at any time, the most appropriate treatment.

PRIMARY CUTANEOUS T CELL LYMPHOMA (PCTCL)

PRIMARY CUTANEOUS T-CELL LYMPHOMA TYPE MF/SS

Introduction

Mycosis fungoides (MF) is the most common form (0,3-0,6/100.000 Hab) of CTCL. Males are more often affected and the incidence of MF is higher among blacks.[5]

It originates from skin-homing T-lymphocytes which, usually, are confined to the skin for an indefinite time. In the early stages, patients have a life expectancy similar to the age-matched general population. Prognosis is significantly altered at the tumoral and advanced nodal stages.[3-5] MF can occur in multiple ways with early stages characterised by limited patches and plaques, often suspicious only for the skilled physician and late stages presenting with tumours, ulceration, systemic involvement or death (*Figure 1*).[5] The phenotype of the malignant clone is compatible with an effector memory T-cell baring additional skin-homing receptors which may explain the long-standing confinement of MF to the skin and, eventually, the skin-draining lymph nodes.

MF is characterised by an infiltrate of α-β T-helper lymphocytes (CD3+, CD4+, CD5+, CD8-) and a minority of cases exhibit a T-cytotoxic or γ-δ T-cell phenotype (CD3+, CD4-, CD5+, CD8+). In general, PD-1 is negative.

Sezary Syndrome (SS) accounts for 5% of CTCL and affects mainly the elderly population (median age of 66 years) with a predominance of males. Caucasians are more likely to be affected.[1] Presentation includes erythroderma with a total body surface involvement of 80% or more and lymph node enlargement. Hyperkeratosis of the palms and soles, hair loss, extensive nail changes and an ectropion can be found. Pruritus is more pronounced than in other forms of CTCL. A central memory T-cell like phenotype is more likely to be found in SS. The diagnosis of SS is based on the presence of a dominant T clone detected in the blood associated with either more than 1000 Sezary cells per mm^3 or loss of expression of a lymphocyte surface antigen (CD7 or CD26), or an elevation of the CD4/CD8 ratio in the blood greater than ten. CD158k/KIR3DL2 has been identified as the most specific marker of Sezary cells. Immunohistology reveals a predominance of T-helper lymphocytes (CD3+, CD4+, CD7-, CD8-). A different expression of PD-1 has been observed in Sezary cells.

Additional subtypes of CTCL are defined in the 2005 WHO and EORTC classification and incorporated into the 2016 revised WHO lymphoma classification (*Table 1*).[1,2] Several clinical and histopathologic variants of MF have been described such as hypopigmented MF, MF palmaris et plantaris, folliculotropic MF, etc. The diagnosis is based on the clinical aspect and confirmed by histology and cytogenetics. Several clinical pictures can be found: discrete fixed erythematous patches in non-photoexposed areas, depilated plaques, cutaneous tumours, follicular hyperkeratosis, unusually placed comedones, and even erythroderma.[1-9] Multiple skin biopsies should be performed. The polymerase chain

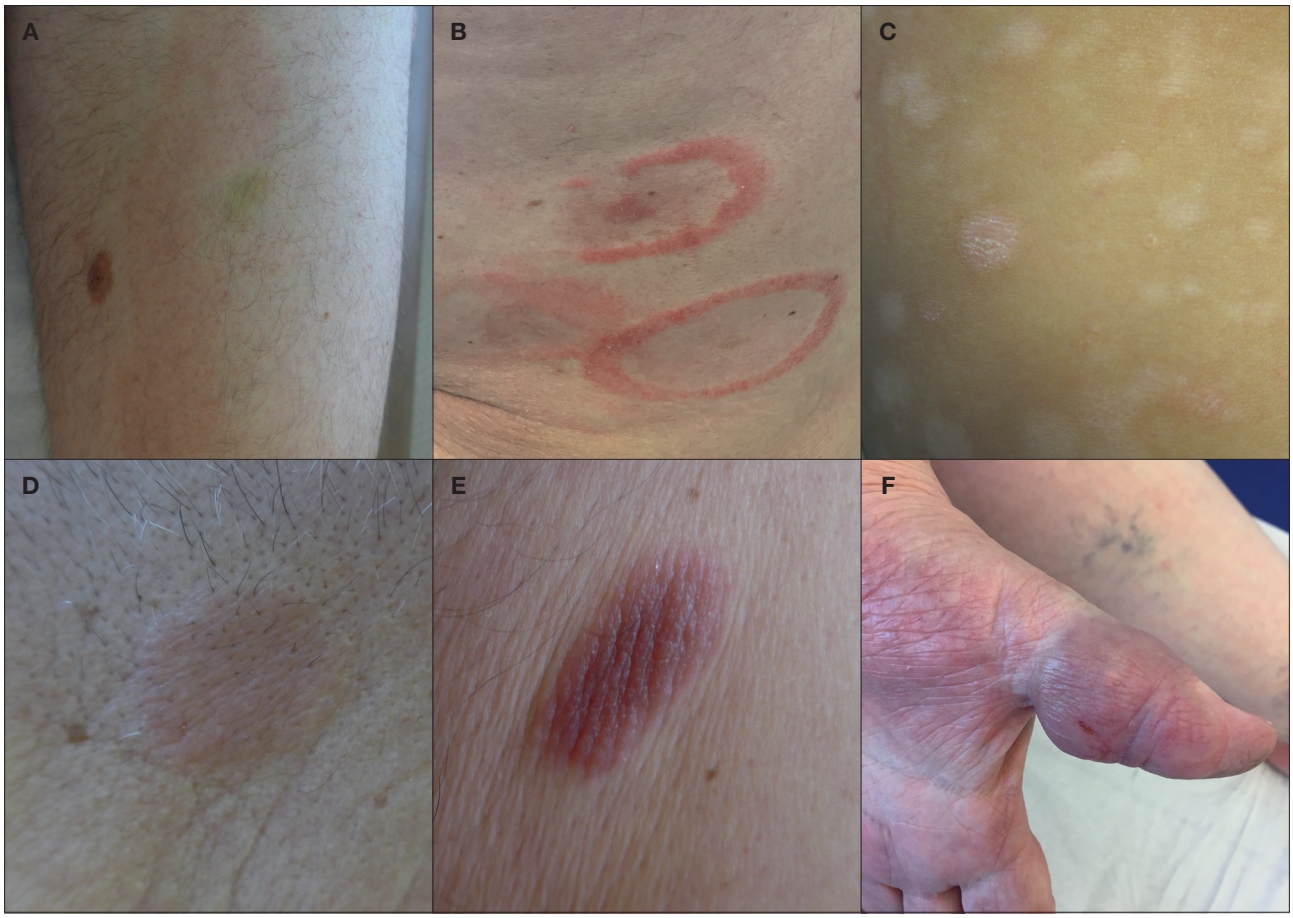

FIGURE 1. Collection of the dermatology department CHU Saint-Pierre, Brussels, Belgium. **(A)** MF, patch stage initial stage; **(B, D, E)** MF, plaque stage; **(C)** Hypopigmented MF; **(F)** MF, tumour stage.

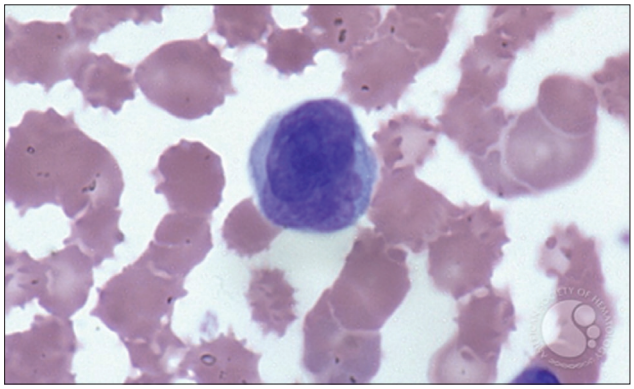

FIGURE 2. Picture from ASH: Sezary cell or cerebriform lymphocyte (hyperconvoluted nuclei).

reaction (PCR) clonality analysis of the T-cell receptor (TCR) gene can help in establishing the diagnosis and up to 60% demonstrate a clonal rearrangement. However, one should keep in mind that clonality does not equal malignancy. Complex abnormalities, losses of TP53, p16ink4a and PTEN genes have been associated with disease progression.

Initial staging

Recommendations for evaluation/initial staging are summarised in *Table 2*.[3] Depending on this initial assessment, the lymphoma stage will be specified in the TNMB classification which shows the extension of the cutaneous lesions and the potential nodal or visceral involvement (*Table 3*).[4,5] These stages correlate with prognosis and they guide therapeutic management.

It is essential to exclude a systemic disease with secondary skin localisation.

Treatment recommendation by disease stages

Table 4 shows the treatments in alphabetical order, their administration and their main side effects.[3-9]

Recommendations for first-line treatment of MF stages IA,IB and IIA:

- *Wait and watch (W&W):* (primarily T1a) is a rational management option because patients with stage IA disease have a low risk of progression and a life expectancy similar to that of an age- and sex-matched population.

TABLE 2. Recommended evaluation/initial staging of the patient with MF/SS.[3,4]

Complete physical examination including
• Description of type(s) of skin lesions, estimate percentage of BSA involved, note any ulceration of lesions, determine total number of tumours and regions involved • Identification of any palpable lymph node (≥1.5 cm in largest diameter) and any organomegaly
Skin biopsy
• Most indurated area if only 1 biopsy, but ideally, do multiple biopsies • Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 should be considered especially in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. CCR4 if mogamulizumab available. CD25 in endemic HTLV-1 area • Evaluation for clonality of TCR gene rearrangement (on paraffin block or fresh tissue)
Blood tests
• Complete blood count (CBC),renal and liver function tests, LDH, comprehensive chemistries • TCR gene rearrangement and relatedness to any clone in skin • Analysis for abnormal lymphocytes by either Sezary cell count (absolute number of Sézary cells) and immuno-phenotyping of circulating CD4+ lymphocytes (CD4/CD8 ratio; CD4+CD7-/CD4+ rate and CD4+CD26-/CD4+ ratio) and if possible the KIR3DL2 phenotype
Radiologic tests
• T_1 et T_2 N_0B_0 : no mandatory imaging but radiologic studies may be limited to a chest radiograph or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy • For other stages : CT scans of chest, abdomen, and pelvis alone +/- 6 FDG-PET (may be used to select the best site to biopsy)
Lymph node biopsy
• Excisional biopsy : in those patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered, or fixed • Site of biopsy: Preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest SUV with a preference for cervical, axillary, and inguinal areas • Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement
Bone marrow biopsy
• Not indicated: it is negative in most cases • Discussed in case of stage B2 or unexplained hematologic abnormalities

- *Skin-directed therapy*
  - Topical corticosteroids (T1a and T2a).
  - Topical Carmustine (BCNU): Currently reimbursed only in the University Hospital of Leuven and the University Hospital of Antwerp.
  - Other interesting therapeutic option: Photodynamic therapy and Imiquimod 5% cream (based on individual case reports).
- *Phototherapy:* UVB is a primary option for the treatment of early MF, particularly stages T1a and T2a, which are characterised by patches only. PUVA is still recommended for plaque disease (T1b, T2b) and for patients with dark skin.
- *Localised radiotherapy (RT):* provides effective palliative treatment for individual lesions and may even induce long-term remission in unilesional disease.

TABLE 3. Staging of mycosis fungoides and Sezary syndrome according to the ISCL-EORTC.[4]

Skin

- T1 Limited patches*, papules, and/or plaques† covering <10% of the skin surface. May further stratify into T1a (patch only) versus T1b (plaque ± patch)
- T2 Patches, papules, or plaques covering ≥ 10% of the skin surface. May further stratify into T2a (patch only) versus T2b (plaque ± patch)
- T3 One or more tumours‡ (≥ 1-cm diameter)
- T4 Confluence of erythema covering ≥ 80% body surface area

Node

- N0 No clinically abnormal peripheral lymph nodes§; biopsy not required
- N1 Clinically abnormal peripheral lymph nodes; histopathology, Dutch grades 1 or NCI LN0-2
- N1a Clone negative#
- N1b Clone positive#
- N2 Clinically abnormal peripheral lymph nodes; histopathology, Dutch grades 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

Visceral

- M0 No visceral organ involvement
- M1 Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)

Blood

- B0 Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells
- B0a Clone negative#
- B0b Clone positive#
- B1 Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
- B1a Clone negative#
- B1b Clone positive#
- B2 High blood tumour burden: ≥ 1000/μL Sezary cells◊ with positive clone#

SS is staged as T4 N2/3/x M0 B2

Clinical stages	T	N	M	B
IA	1	0	0	0.1
IB	2	0	0	0.1
IIA	1.2	1.2	0	0.1
IIB	3	0-2	0	0.1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA1	1-4	0-2	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

** For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.*

† For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (.25% large cells), CD301 or CD302, and clinical features such as ulceration are important to document.

‡ For skin, tumour indicates at least one 1-cm diameter solid or nodular lesion 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 of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

§ For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed, or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

¶ For viscera, spleen and liver may be diagnosed by imaging criteria.

◊ For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumour burden for B2, then 1 of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: 1) expanded CD41 or CD31 cells with CD4/CD8 ratio of 10 or more, (2) expanded CD41 cells with abnormal immunophenotype including loss of CD7 or CD26.

 # A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

Recommendations for second-line treatment of MF stages IA, IB and IIA:

- *Systemic therapies*
  - Interferon-α (IFN-α).
  - Bexarotene: a selective retinoid X receptor agonist: in Belgium, bexarotene can only be prescribed if the patient has had prior treatment with interferon.
  - These agents are most commonly combined with PUVA with a higher complete remission rate.
- *Total skin electron beam therapy (TSEB):* (mainly T2b) (Available only in Namur, Leuven and Gent).
- *Low-dose Methotrexate (MTX)*

Recommendations for first-line treatment of MF stages IIB:

- *Systemic therapies*
  - IFN-alpha
  - Bexarotene
  - Commonly combined with PUVA
- *TSEB*
- *Monochemotherapy*
  - Gemcitabine
  - Pegylated liposomal doxorubicin
- *Low-dose MTX*
- *Localised RT:* only in combination with systemic and other skin directed therapies.

Recommendations for second-line treatment of MF stages IIB:

- *Polychemotherapy:* is used as a last resort, except for palliative or prior to therapeutic intensification with allograft discussion.
  - CHOP: cyclophosphamide - doxorubicin - vincristine - prednisolone is the most widely used regimen in advanced stages.
- *Allogeneic stem cell transplantation:* in selected patients, the only curative option.

Recommendations for first-line treatment of MF stages IIIA and B:

- *Systemic therapies*
  - IFN-alpha
  - Bexarotene
  - Commonly combined with PUVA
- *Extracorporeal photochemotherapy (ECP):* can be used alone or in combination with other therapies (but not reimbursed in CTCL in Belgium).
- *Low-dose MTX*
- *TSEB*

Recommendations for second-line treatment of MF stages IIIA and B:

- *Monochemotherapy*
  - Gemcitabine
  - Pegylated liposomal doxorubicin
- *Allogeneic stem cell transplantation*

Recommendations for treatment of MF stages IVA and IVB:

- *Chemotherapy*
  - Gemcitabine
  - Pegylated liposomal doxorubicin
  - CHOP or CHOP-like polychemotherapy (CHOEP with Etoposide for an example).
- *Radiotherapy (TSEB and localised):* alone or with systemic therapies.
- *Alemtuzumab (mainly in B2):* humanised monoclonal antibody (IgG1) against CD52 (not available anymore in Belgium).
- Allogeneic stem cell transplantation

Recommendations for first-line treatment of SS:

- *ECP:* alone or in combination with other therapies.
- *Chlorambucil + prednisone*
- *Systemic therapies in combination with ECP or PUVA*
  - IFN-alpha
  - Retinoids
- *Low-dose MTX*

Recommendations for second-line treatment of SS:

- *Chemotherapy*
  - Gemcitabine
  - Pegylated liposomal doxorubicin
  - CHOP or CHOP-like polychemotherapy
- *Alemtuzumab*
- *Allogeneic stem cell transplantation*

Agents that can be used for maintenance after remission in MF and SS:

ECP, IFN-alpha, Low-dose MTX , PUVA, Retinoids, Topical corticosteroids, and UVB.

New promising drugs

New therapies are described in another issue of the Belgian Journal of Haematology (2017).[7]

These new therapies are not yet reimbursed in CTCL in Belgium:

- *Histone deacetylase inhibitors (vorinostat and romidepsin)*
- *Monoclonal antibodies (brentuximab vedotin, mogamulizumab, pembrolizumab)*

- *Proteasome inhibitor (bortezomib)*
- *Alkylating agents (temozolomide)*
- *Immunomodulatory agents (lenalidomide)*
- *New check Point inhibitors (Anti-PD1, Anti-PDL-1)*

PRIMARY CUTANEOUS CD30+ LYMPHOPROLIFERATIVE DISORDERS (CD30+LPD)

Introduction

CD30+ LPDs are the second most common form of CTCL and include lymphomatoid papulosis (LyP), primary cutaneous anaplastic large-cell lymphoma (cut-ALCL) and borderline cases.[10]

Multiple papulo-nodular lesions occurring in spontaneously regressive flares are typical of LyP, while rapidly enlarging skin nodules and plaques with necrosis are seen in cut-ALCL (*Figure 2*).[1-10] Diagnosis depends on confrontation of histology with the clinical picture. Diagnostic criteria are listed in *Table 5*.[10] It is very difficult to differentiate cut-ALCL from a transformed mycosis fungoides. The clinical history (absence of known MF, presentation with ulcerated nodular lesions, etc.) and the positivity of IRF4 will be in favour of cut-ALCL.[15]

A systematic biological or radiological work-up is not recommended in LyP. *Table 6* summarises the recommendations on evaluation/initial staging and *Table 7* shows the EORTC/ISCL TNM classification of non-MF/SS cutaneous lymphomas.[10,11] CD30+ LPDs have an excellent prognosis.

Treatment recommendation by disease stages[7-10]

Table 4 shows the treatments in alphabetical order, their administration and their main side effects.[3-9]

Lymphomatoid papulosis

- *First-line*
  - W&W in first intention: because lesions are spontaneously regressive.
  - Topical corticosteroids: can accelerate regression but do not prevent the appearance of new lesions.
  - PUVA therapy or UVB: for multiple or disabling lesions.
- *Second-line*
  - MTX
  - IFN-alpha (not reimbursed in Belgium for this indication)
  - Bexarotene (not reimbursed in Belgium for this indication)
- *Third-line:* Brentuximab (not reimbursed in Belgium)

Primary cutaneous anaplastic large-cell lymphoma

- *W&W:* because complete spontaneous regression is observed in 30% of cases.

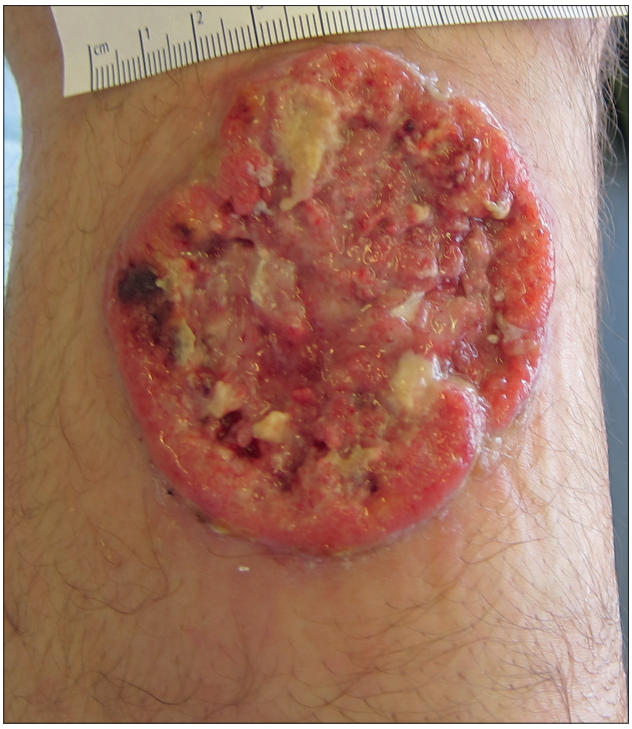

FIGURE 3. From the dermatology department CHU Saint-Pierre, Brussels, Belgium. Cutaneous anaplastic large-cell lymphoma.

- *Progressive cutaneous lesions:*
  - T1a, T1b, T2a: RT or surgical excision (if less than five tumours).
  - >T2a:
  » First-line: MTX
  » Second-line: IFN-alpha
  » bexaroten
  » brentuximab (Early access program)
  - Node involvement or other extracutaneous involvement:
  » Polychemotherapy (CHOP)
  » Allogeneic stem cell transplantation

PRIMARY CUTANEOUS B CELL LYMPHOMA (PCBCL)

INTRODUCTION

Primary cutaneous B-cell lymphomas (CBCL) are a heterogeneous group that represent 20-25% of cutaneous lymphomas. Three main types are recognised: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle centre lymphoma (PCFCL) and primary cutaneous large B-cell lymphoma (PCLBCL), leg type. This review provides practical guidelines for the management and treatment of PCBCLs. Intravascular large B-cell lymphoma (IVLCL), will also be discussed.[1,2,12-15]

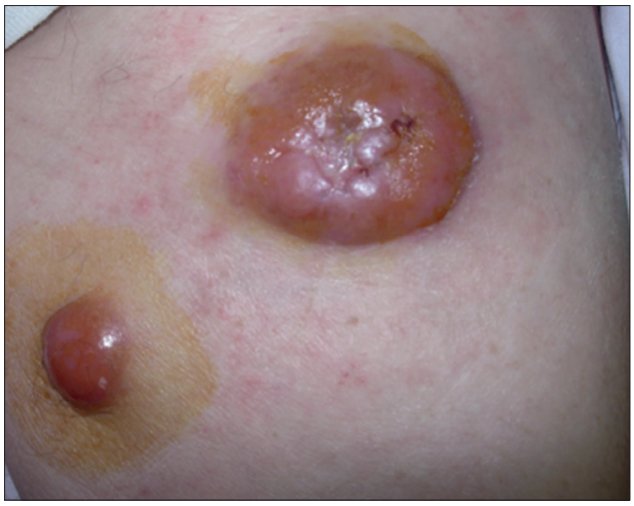

FIGURE 5. Collection of the dermatology department CHU Saint-Pierre, Brussels, Belgium. Cutaneous large B cell lymphoma, leg type.

By definition, a primary cutaneous B-cell lymphoma is N0, M0 at diagnosis.[11] An extensive review on PCBCL is published in another issue of this journal in 2017 by Willemze.[17]

DIAGNOSTIC TOOLS AND STAGING

French recommendations have proposed an algorithm for the management of skin lesions suspected to be B-cell lymphoma.[12] The purpose is to eliminate the differential diagnoses of benign lymphocytic hyperplasia and cutaneous localisation of systemic B-cell lymphoma. *Table 8* summarises the recommendations for evaluation and staging.

Primary Cutaneous Marginal Zone B-cell Lymphoma (PCMZL)

Introduction

Primary cutaneous marginal zone lymphoma (PCMZL) is an indolent lymphoma composed of small B lymphocytes. It affects young adults with a male predominance and presents with solitary or, more commonly, multifocal red to violaceous papules, plaques or nodules localised preferentially to the trunk and arms. Cutaneous relapses are common, in particular in patients presenting with multifocal skin lesions. Dissemination to extra-cutaneous sites is rarely observed. PCMZL may develop from chronic antigenic stimulation by intradermal applied antigens, e.g. tattoo pigments, tick bites and antigen injections. Borrelia (B) burgdorferi infection has been reported in a minority of cases of PCMZL, and Borrelia PCR on skin lesions is therefore recommended. The neoplastic cells express the B-cell-associated antigens CD20 and CD79a. They are Bcl-2-positive but do not express CD5, CD10 or Bcl-6. Differentiation between PCMZL and cutaneous pseudo-B-cell lymphoma (cutaneous lymphoid hyperplasia) can be difficult. Demonstration of plasma cells expressing monoclonal kappa or lambda light chains is very useful.

Clonal rearrangements of the immunoglobulin heavy chain (IgH) are found in most cases. Translocation t(14;18) is found in ≤ 25% of PCMZL, t(11;18) in 7% of cases and t(3;14) in 10%.[14,15]

PCMZL has an indolent clinical course. The prognosis is excellent with a 5-year disease-specific survival rate close to 100%.

Treatment[12-18]

Solitary/localised skin lesions

- *Local RT*
- *Surgical excision*
- *Antibiotics doxycycline or cephalosporin:* in patients with an associated B. burgdorferi.
- *Select cases/observation:*
  - Topical therapy: steroids, imiquimod
  - Intralesional steroids
  - Intralesional IFN-α
  - Intralesional rituximab

Multifocal skin disease or relapsing disease

- *Wait and see strategy*
- *For symptomatic lesions*
  - Topical or intralesional steroids
  - Intralesional IFN-α
  - Intralesional rituximab
  - Low-dose RT
- *Polychemotherapy:* for rare patients developing extracutaneous disease.
  - CHOP +/- rituximab (R-CHOP)

Primary Cutaneous Follicular cell Lymphoma (PCFCL)

Introduction

PCFCL affects middle-aged adults and has a male predominance. It presents with solitary or grouped plaques and tumours, preferentially located on the scalp or forehead or trunk, uncommonly on the legs. Multifocality of skin lesions (15% of patients) is not associated with a more unfavourable prognosis. Involvement of extracutaneous sites is uncommon.[14]

The neoplastic cells express the B-cell-associated antigens CD20 and CD79a, as well as the follicle centre cell markers CD10 and BCL6. Unlike nodal FCL, PCFCL is mostly BCL2-negative or shows only faint BCL2 staining. Paired box gene (PAX-5 and IRF8 are usually expressed, but other B cells are positive as well. The multiple myeloma oncogene-1 (MUM-1) is negative but some scattered cells may be positive (<30%).

TABLE 4. Summary of treatment options for cutaneous lymphomas, their administrations terms and their secondary effects.[3-9]

Therapy	Management	Comment including potential toxicities
Alemtuzumab (not available anymore in Belgium)	IV 30mg 3x/w 12w	Infections (CMV reactivation), haematological toxicity
Alkylating agents: Temozolomide	Po 75mg/m² x 42 d + Maintenance	Haematological toxicity, liver toxicity
Bexarotene	Po 300mg/m²/d (starting gradually, usually at 150mg/m²/d)	Drying skin and mucous membranes - rash, headache, elevated blood lipids (cholesterol and triglycerides) requiring fibrates or statins treatment, central hypothyroidism requiring thyroid hormone substitution
Chlorambucil + prednisone	Po continuous treatment : 2-6mg/d of chlorambucil + 20mg/d of prednisone (to be reduced to 0-10mg/d)	Myelosuppression, leukemogenic risk
Extracorporeal photo-chemo-therapy	2 sessions/month	Infections
Histone deacetylase inhibitors • Vorinostat • Romidepsin	• Po 400mg/d • IV 14mg/m2 d1, d8, d15 /28 d	• Asthenia, anorexia, diarrhoea, haematological toxicity • Nausea, anorexia, vomiting
Immunomodulatory agents: • Lenalidomide	Po 15-25mg X 21d /28d	Asthenia, infections, leukopenia, venous thromboembolism
Interferon-α	• Sc 3-6 million units : 3x/w or d for CTCL • IL 1-6 million units : 3x/w for CBCL	Flu-like symptoms, elevated transaminases, leukopenia, thrombocytopenia, mental depression, cardiac arrhythmias, thyroid dysfunction
Localised radiotherapy	• 0.7 to 35 Gy and may be fractionated for CTCL • 30 Gy in 3-4 w for CBCL • 2x 2 Gy for palliative dose	Alopecia in case of scalp injury
Methotrexate	Po or IM 20-30mg 1x/w	Cytopaenia, long-term risk of liver disease : protective effect of folic acid supplementation

Clonally rearranged immunoglobulin genes are present but PCFCL does not, or rarely, carry the (14;18) translocation, which is characteristically found in nodal follicular lymphomas.[14,15]

Treatment[12-18]

Solitary / localised skin lesions

- *Local RT*
- *Surgical excision: for small solitary lesions*

TABLE 4. *Continuation.*

Therapy	Management	Comment including potential toxicities
Monochemotherapy • Gemcitabine • Pegylated liposomal doxorubicin	• IV 800-1200mg/m² on d 1, 8 and 15 of a 28-d cycle for 4 cycles • IV 20mg/m² on d 1 and 15 of a 28-d cycle for 6 cycles	Haematological toxicity, infections, skin flare
Monoclonal antibodies • Brentuximab Vedotin (anti-CD30) • Mogamulizumab (anti-CCR4) • Pembrolizumab (anti-PD1)	• IV 1,8mg/kg/3 w x 8 cycles • IV 1mg/kg 1x/w 4w and after 1x/2w • IV 2mg/kg/3 w	• Polyneuropathy neutropenia, nausea • Nausea, headache, infusion reactions • Cutaneous flair effect (SS), immune toxicity
Phototherapy • UVB • PUVA	Requires regular 2-3 x /w treatment	Risk of skin cancers with cumulative dosing
Polychemotherapy • CHOP • CHOP-like (R-CHOP, R-mini-CHOP, CHOEP, etc.)		Myelosuppression
Proteasome inhibitor: Bortezomib	IV 1,3mg/m² d1, 4, 8, 11 /21d	Polyneuropathy, thrombocytopenia, neutropenia
Rituximab	• IV 375mg/m² 1x/w 4-8w • IL 10 mg/lesion 3x in a single w at monthly intervals	• Fever • Localised pain at the injection, urticaria, fever, and transient rash, nausea and malaise
Topical Carmustine	3-5 whitewashes/w until a remission (preparation: 100mg of Carmustine in 250 g paraffin / petrolatum 20/80)	Irritant contact dermatitis
Topical corticosteroids (Class I)	1-2x/d (+/- 5g/d)	Toxicities if extensive skin application for long periods
Total skin electron beam therapy	30-36 Gy for 8-10 w	Higher doses associated with acute skin toxicities

IV, intravenous; PO, per os; w, week; d, day; IL, intralesional; SC, subcutaneous;

- *Select cases/observation:*
  - Topical therapy: steroids, imiquimod
  - Intralesional steroids
  - Intralesional IFN-α
  - Intralesional rituximab

Generalised skin disease or relapses

- *Wait and see strategy*
- *For symptomatic lesions*
  - Topical or intralesional steroids
  - Intralesional IFN-α
  - Intralesional rituximab

TABLE 5. Diagnostic criteria for CD30 LPD.[10-15]

A. LyP	B. Cut-ALCL
Clinical criteria	
• Recurrent self-healing grouped or disseminated papulo-nodular skin lesions • Note: Self-healing is defined as spontaneous regression of each individual tumour lesion within weeks or months, whether or not new lesions occur • LyP may manifest concurrently with MF, which is typically characterised by patches and eventually plaques or tumours	• Solitary, grouped, or multifocal nodular lesions • No clinical evidence of LyP, MF, or other types of CTCL • Absence of extracutaneous involvement assessed by staging procedures
Histologic criteria	
• LyP type A ("conventional" type): Wedge-shaped infiltrate with scattered or clustered CD30+ tumour cells, intermingled with numerous inflammatory cells, such as small lymphocytes, neutrophils, eosinophils, and histiocytes. This is the most frequent histologic presentation • LyP type B (mycosis fungoides-like): Epidermotropic infiltrate of small atypical CD30+ or CD30- lymphoid cells with cerebriform nuclei that histologically resembles MF • LyP type C (anaplastic large cell lymphoma-like): Nodular infiltrate with sheets of cohesive CD30+ large atypical lymphoid cells with only a few admixed reactive inflammatory cells (small lymphocytes, neutrophils and eosinophils) • LyP type D (cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma-like): Epidermotropic infiltrate of small- to medium-sized atypical CD8+ and CD30+ lymphoid cells • LyP type E (angiocentric/angiodestructive): Angiotropism with angiodestruction. CD30 and sometimes CD56 are expressed by the neoplastic cells • Immunophenotypically, CD30+ tumour cells express CD4+ in most cases, but CD8+ or CD56+ phenotypes have been reported. T-cell-associated antigens, such as CD45RO, are expressed with variable loss of pan-T-cell antigens (CD2, CD3, CD5) in LyP • Note: There is a broad differential diagnosis because the presence of large atypically appearing CD30+ lymphoid cells is not restricted to CD30 LPD but is seen in various inflammatory and infectious disorders	• Dense nodular dermal infiltrate composed of large pleomorphic, anaplastic, or immunoblastic cells with large, irregularly shaped nuclei and abundant pale or eosinophilic cytoplasm. Clusters of small reactive lymphocytes and eosinophils may be found within and surrounding the tumour cells • Immunophenotypically, CD30+ is expressed by at least 75% of tumour cells. In addition, CD4 or CD8 is expressed in most cases with variable loss of pan-T-cell antigens (CD2, CD3, CD5) • Note: In contrast to nodal ALCL, primary cutaneous forms of ALCL lack epithelial membrane antigen and express the cutaneous lymphocyte antigen (HECA-452). Anaplastic lymphoma kinase ALK-1 (p80) and t(2;5) translocation are usually absent in Cut-ALCL. If these are present, one needs to be highly suspicious of the lesions being a cutaneous manifestation of underlying systemic ALCL

- *Low-dose RT*
- *Intravenous or intralesional rituximab*
- *Polychemotherapy: CHOP / R-CHOP*

Cutaneous Large B cell Lymphoma, leg type

Introduction

PCLBCL affects elderly patients and particularly females. Patients present with rapidly growing red or bluish-red tumours on one or both legs. Uncommonly, skin lesions can arise at sites other than the legs. PCLBCL with a predominance of centroblasts and immunoblasts, usually present with skin lesions on the (lower) legs. In contrast to PCFCL and PCMZL, these lymphomas often disseminate to extracutaneous sites and have an unfavourable prognosis.

TABLE 6. Diagnostic workup of CD30 LPD.[10]

History
• Wax and waning of lesions (i.e., spontaneous regression of each lesion within weeks to months) with new ones developing • Previous lymphoid neoplasms, particularly Hodgkin lymphoma, nodal anaplastic large cell lymphoma, and MF • Immunosuppression (HIV, organ transplantation, or other conditions associated with immunosuppressive therapy, immunosuppression-related CD30 LPDs) • B symptoms (fever, night sweats, weight loss)
Physical examination
• Size and number of lesions • Presence of patches and/or plaques indicates possibility of associated MF • It is necessary to differentiate MF with transformation (CD30 may be expressed by large tumour cells in transformed MF) from CD30 LPD • Enlarged lymph nodes • Hepatic or splenic enlargement
Laboratory investigations
• Complete blood cell count and differential • Blood chemistries, including LDH • Serology for HTLV-1/2 (only in areas with endemic HTLV infection) to identify adult T-cell lymphoma/leukaemia, in which expression of CD30 by tumour cells can occur
Radiologic examinations
• LyP: Radiologic examinations (chest x-ray, ultrasound abdomen and pelvis, or CT scan) are considered as optional examinations in patients with typical LyP and absence of palpable enlarged lymph nodes, absence of hepatosplenomegaly, normal laboratory tests, and absence of B symptoms • Cut-ALCL: Contrast-enhanced CT scan with or without positron emission tomography (chest, abdomen, pelvis) or whole-body integrated positron emission tomography/CT
Bone marrow aspirate or biopsy
• LyP: Not performed in patients with typical LyP • Cut-ALCL: Optional in patients with solitary Cut-ALCL or patients with Cut-ALCL without extracutaneous involvement in radiologic examinations • Lymph node biopsy: If enlarged lymph nodes (defined as 1.5 cm in greatest transverse long axis diameter) are palpable or enlarged lymph nodes are detected on radiologic examination

The neoplastic cells are predominantly centroblasts and immunoblasts. They express B-cell-associated antigens (non GCB phenotype) CD20 and CD79a and are strongly expressed for BCL2, BCL6, MUM1, FOXP1, MYC and cytoplasmic IgM. CD10 is generally negative. Ki-67 positivity is present in more than 75% of the cells. PCLBCL has a poor prognosis with 5-year survival rates of 50%.[14,15]

Treatment[11-18]

Solitary / localised skin lesions

- *Multi-agent chemotherapy (R-CHOP) +/- RT:* is the reference treatment.

In patients ineligible (for multiagent chemotherapy) because of age and/or comorbidities.

TABLE 7. ISCL/EORTC proposal on TNM classification of cutaneous lymphoma other than MF/SS.[11]

T: Skin
• T1: Solitary skin involvement - T1a: a solitary lesion < 5 cm diameter - T1b: a solitary > 5 cm diameter • T2: Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions - 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 • T3: Generalised skin involvement - T3a: multiple lesions involving 2 non contiguous body regions - T3b: multiple lesions involving ≥ 3 body regions N
N: Node
• N0: No clinical or pathologic lymph node involvement • N1: Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement • 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 • N3: Involvement of central lymph nodes
M: Visceral
• M0: No evidence of extracutaneous non-lymph node disease • M1: Extra cutaneous non-lymph node disease present

- *Local radiotherapy*
- *R-mini-CHOP*: reduced doses of anthracyclines.
- *Novel drugs targeting:* different components of the NF-kB pathway are currently under investigation (Bortezomib, Lenalidomide).

Intravascular large B cell lymphoma (IVLBCL)

Introduction

IVLBCL results from malignant lymphocyte proliferation taking place in the lumen of all medium and small calibre vessels except lymphatics. This lymphoma primarily affects an older population with a median age of 67 years (34-90 years).[17] The clinical presentation is polymorphic and usually includes severe general symptoms (fever, progressive asthenia, weight loss, night sweats, pain). Skin lesions may look like an indurated erythematous eruption, violaceous or erythematous plaques, nodules, discolorations, cellulitis or small red palpable spots, etc.

Neoplastic cells are positive for B-cell-associated markers (CD20, CD79a), in a subset of cases show aberrant CD5 expression and positive for Bcl-2 and MUM-1. But they are negative for Bcl-6 and CD 10.

Prognosis is poor, but some investigators have described a more indolent behaviour when only the skin is affected.[17,18]

Treatment[17,18]

Multi-agent chemotherapy (R-CHOP) with/without allo-geneic stem cell transplantation.

CONCLUSION

This paper focuses on staging and treatment of cutaneous T and B-cell lymphomas according to Belgian reimbursement. Management of cutaneous lymphoma requires the expertise of a multidisciplinary team to optimize the diagnosis, treatment and supportive care of these patients. Many patients at early stages require only topical treatment but other need systemic immuno and/or chemotherapy. Radiation therapy is also useful in selected cases.

TABLE 8. Recommended evaluation/staging of patient with PCBCL.[11-15]

History
• B signs: asthenia, weight loss, night sweats • Drugs, bites, tick bites, etc.
Complete physical examination
• Number, topography and extent of skin lesions • Presence or absence of lymphadenopathy/organomegaly
Skin biopsy
• Immunophenotyping: - Differentiation markers B and T: CD20, CD19, CD3, CD79a - Differentiation markers of the follicular centres: Bcl6, CD10 - Bcl-2: often negative in PCFCL - Light chains of immunoglobulin for plasma cell differentiation: monotypic in PCMZL - Mum-1/IRF4 for large cells CBCL - PAX 5/IRF8 for PCFCL - CD23, CD21, Ki67: useful for distinguishing benign and neoplastic follicular structures - CD5: systemic lymphomas • Evaluation for clonality of immunoglobulin heavy and light chains rearrangement • FISH or PCR: translocation (t) (14,18) (q32;q21) if there is doubt between PCFCL and cutaneous localisation of systemic follicular lymphoma. Some PCFCL may harbour Bcl2 translocation and are not systemic. So if a Bcl2 translocation should raise the awareness of a possible systemic FL, it can still be a localised one
Laboratory investigations
• Blood count, liver function, serum protein electrophoresis, LDH, β2-microglobulin • Search for a blood monoclonal B population by flow cytometry or PCR
Radiologic examinations
• Chest x-ray, ultrasound abdomen and pelvis, or CT scan
Bone marrow biopsy (with cytology, flow cytometry and genetic examination in case of involvement)
• PCMZL: in cases of visceral or lymph node involvement • PCFCL: systematically • PCDLBCL: not recommended but may be discussed case by case

Noteworthy, many promising drugs (conjugated anti CD30 antibodies, anti PD1, PDL1, etc.) achieve up to 50% of CR in CTCL subtypes such as MF, SS and CD30+ cutaneous lymphoma. Reimbursement in these indications is thus eagerly awaited also in Belgium.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.

2. Swerdlow S, Campo E, Pileri S, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Cutaneous lymphomas must be managed by a multidisciplinary team.**

2 **New promising drugs such as Brentuximab Vedotin or anti-PD1 antibodies are not yet reimbursed in Belgium.**

3 **Allogeneic stem cell transplantation remains a curative treatment in highly selected 'fit' patients.**

3. Whittaker S, Hoppe R, Prince M. How I treat mycosis fungoides and Sézary syndrome. Blood. 2016;127(25):3142-53.

4. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110(6):1713e22.

5. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer. 2017;77:57-74.

6. Scarisbrick JJ, Prince M, Vermeer MH, et al, Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol. 2015;33(32):3766-73.

7. Bron D, Springael C, Maerevoet M, et al. New therapeutic approaches in cutaneous T-cell lymphomas. Belg J of Hematol. 2017;8(3):102-6.

8. Beylot-Barry M, Dereure O, Vergier B, et al. [Management of cutaneous T-cell lymphomas: Recommendations of the French Cutaneous Lymphoma Group]. [Article in French]. Ann Dermatol Venereol. 2010;137(10):611-21.

9. Foss F, Girardi M. Mycosis Fungoides and Sezary Syndrome. Hematol Oncol Clin N Am. 2017(31):297-315.

10. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;118:4024-35.

11. Kim Y, Willemze R, Pimpinelli N. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110:479-84.

12. Grange F, D'Incan M, Ortonne N, et al. [Management of cutaneous B-cell lymphoma: recommendations of the French cutaneous lymphoma study group]. [Article in French]. Ann Dermatol Venereol. 2010;137(8-9):523-31.

13. Senff N, Noordijk EM, Kim Yh, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood. 2008;112:1600-9.

14. Suarez AL, Pulitzer M, Horwitz S, et al. Primary cutaneous B-Cell Lymphomas: Part I Clinical features, diagnosis, and classification. J Am Acad Dermatol. 2013;69:329.e1-13.

15. Cerroni L. Skin Lymphoma: the illustrated guide - Fourth edition 2014.

16. Suarez AL, Querfeld C, Horwitz S, et al. Primary cutaneous B-Cell Lymphomas: Part II Therapy and future directions. J Am Acad Dermatol. 2013;69:343.e1-11.

17. Ferreri AJM, Campos E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases with special emphasis on the «cutaneous variant». Br J Haematol. 2004;127:173-83.

18. Willemze R. Primary Cutaneous B-cell lymphomas. Belg J Hematol. 2017(8):213-21.