short review

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Cutaneous lymphomas—fast facts about an orphan disease—a short review

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Summary Cutaneous lymphomas are a rare group of primary skin lymphoproliferative disorders, divided into T and B cell lymphomas. They differ substantially in clinical course and therapy. The two main subtypes of primary cutaneous T-cell lymphomas include mycosis fungoides, which is the most common, and Sézary syndrome, the rare leukemic variant. Skin lesions seen in mycosis fungoides patients are erythematous patches, plaques, or tumors. Most patients remain at patch/plaque (early) stage, while some progress to tumor (advanced) stage during their clinical course. Sézary syndrome is characterized by erythroderma and involvement of lymph nodes and the peripheral blood. Treatment is dependent on the disease stage. Therapeutic options include skin-directed and systemic therapies. In localized, early stage mycosis fungoides, prognosis is usually good which changes in advanced stages. Significant progress has been made in recent years in the clinical management of progressive or relapsed cutaneous T-cell lymphomas by the approval of new targeted therapies. Although there are no curative treatment options apart from allogeneic transplantation, response rates are often encouraging, in particular when using combination therapies. Primary cutaneous B cell lymphomas are rare and three main subtypes are recognized: primary cutaneous marginal zone lymphoma, primary cutaneous follicle center lymphoma, and primary cutaneous diffuse large B-cell lymphoma, leg type. An accurate diagnosis of the subtype is important for therapeutic management. The most common clinical presentations are red-to-violaceous cutaneous nodules and papules. Primary cutaneous marginal and follicle center lymphoma have excellent 5-year survival rates of 95–99%.

Keywords Primary cutaneous T cell lymphomas · Primary cutaneous B cell lymphomas · Mycosis fungoides · Clinical course · Therapy

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Background

Cutaneous lymphomas (CL) are a heterogenous group of lymphoproliferative disorders of the skin with variable clinical presentations and courses. They are categorized as extra-nodal non-Hodgkin lymphomas and they are the second most common form in this group, after mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach [1, 2].

Primary CLs comprise a large spectrum with ~75% diagnosed as primary cutaneous T cell lymphomas (CTCL) and ~25% as primary cutaneous B cell lymphomas (CBCL) [1–3].

The incidence is rare—European data suggest an incidence of ~1 per 100,000 persons for all CLs [4] and an incidence of 0.29–0.39 per 100,000 persons for CTCLs, respectively [5].

CLs are classified according to the current World Health Organization (WHO)/ European Organization of Research and Treatment of Cancer (EORTC) classification [2, 6, 7]. An overview of the classification of CTCL and CBCL is shown in Table 1.

There are several different CTCL subtypes, with mycosis fungoides (MF) being the most frequent CTCL variant. Sézary syndrome (SS), which is a leukemic and aggressive MF-variant, is much rarer (0.1 per 1,000,000 persons) [8]. An overview of the variants is shown in Table 1.

Table 1 Classification of primary cutaneous lymphomas (CL)— 2018 WHO/EORTC update [2]

Primary cutaneous T-cell lymphomas	Primary cutaneous B-cell lymphomas
Mycosis fungoides	Primary cutaneous marginal zone B-cell lymphoma
Mycosis fungoides variants Folliculotropic mycosis fungoides Pagetoid reticulosis Granulomatous slack skin	Primary cutaneous follicle center lymphoma
Sézary syndrome	Primary cutaneous diffuse B-cell lymphoma, leg-type
Adult T-cell leukemia/lymphoma	*EBV*+ mucocutaneous ulcer (provisional)
Primary cutaneous CD30+ lymphoproliferative disorders Primary cutaneous anaplastic large cell lymphoma Lymphomatoid papulosis	Intravascular large B-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma	–
Extra-nodal natural killer/T-cell lymphoma, nasal-type	–
Chronic active EBV infection	–
Primary cutaneous peripheral T-cell lymphoma, rare subtypes Primary cutaneous γ/δ T-cell lymphoma Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional) Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional) Primary cutaneous acral CD8+ T-cell lymphoma (provisional)	–
Primary cutaneous peripheral T-cell lymphoma, not otherwise specified	–

World Health Organization/European Organization of Research and Treatment of Cancer (WHO/EORTC) classification of primary CLs, modified after Willemze et al. [2]
EBV Epstein–Barr virus

Cutaneous T cell lymphomas—mycosis fungoides (MF)

Fig. 1 shows typical skin lesions that may be present in a patient with mycosis fungoides (MF). Apart from pruritus, which is a common symptom in about 66% of patients with MF, the lesions are asymptomatic. At initial diagnosis, about 70% of MF patients present with less than 10% of involved body surface area, which corresponds to early stage disease IA–IIA [9]. Retrospective analyses reported that about one third of patients present initially with advanced stages (stages IIB–IVB), which is a strong negative prognostic factor in MF patients. [9, 10].

Patients with MF do typically show patches and/or plaques, in advanced stages tumors might develop (Fig. 1c). Interestingly, the different skin stages (patch, plaque, tumor) may occur simultaneously or individual skin stages can be skipped, which does sometimes lead to various morphological pictures [11].

Erythroderma, defined as diffuse erythema and scaling confined to at least 80% of the body surface area, is often the clinical presentation of advanced-stage MF, but it is also common in patients with Sézary syndrome (SS; Fig. 1d). An exact diagnosis and staging are important in patients presenting with MF/SS, as prognosis and treatment recommendations vary widely [1, 2, 10, 11]. Staging is performed using a revised TNM classification, which also includes prognostic factors. Table 2 gives an overview of revised, updated TNMB classification [6, 12]. Staging and subsequent treatment planning usually include the following: the exact clinical examination and documentation of the skin lesions, histological interventions (including immune phenotyping and clonality testing), laboratory results and diagnostic imaging such as sonography of lymph nodes and/or abdomen and/or whole-body computed tomography, depending on the initial clinical presentation.

Advanced-stage disease is associated with a poor prognosis and a 5-year disease-specific survival (DSS) rate of 0–40% [9–11, 13]. Apart from the clinical stage at the time of diagnosis, other independent negative prognostic markers have been identified, such as age older than 60 years, large cell transformation, an increased lactate dehydrogenase and stage IV disease [14]. Independent of the disease stage, MF patients do have an increased risk to develop a second hematological neoplasm, and a higher risk for solid tumors [15].

Sézary syndrome (SS) has been defined as an independent leukemic entity with erythroderma, generalized lymphadenopathy and the presence of neoplastic tumor cells with atypical lymphocytes with cerebriform nuclei (Sézary cells) [1, 2, 6, 13]. SS is associated with a median survival between 2 and 4 years and a 5-year DSS of about 36% [2, 3, 6, 11, 12].

Etiology and pathogenesis

The etiopathology of CTCLs is still unclear, although several possible reasons have been discussed such as geographical, pollution, viral infections [16].

In the majority of cases (>90%), MF and SS originate from distinct “skin-homing” CD4+ T-cell populations [17]. In patients with localized disease, it is assumed that the adaptive immune response has a surveillance function and might control disease progression over years [17, 18]. In advanced-stage disease (IIB–IVB), it is hypothesized that the tumor microen-

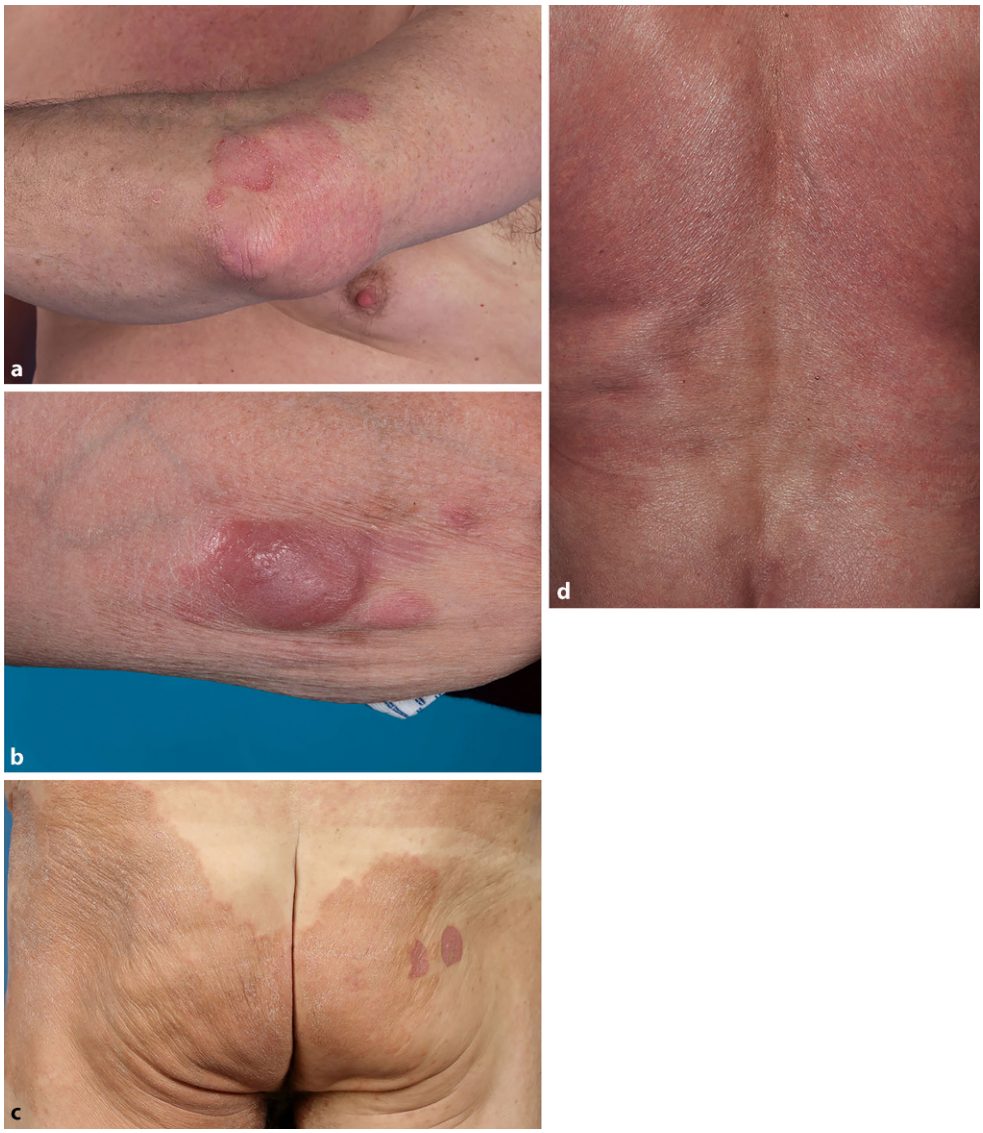

Fig. 1 **a–d** Typical clinical picture of a primary cutaneous T cell lymphoma with patches and plaques on the elbow and gluteal region (**a**,**c**), tumors (**b**) and erythroderma (**d**)

Table 2 Clinical staging of Mycosis fungoides (MF) and Sézary syndrome (SS), modified from the International Society for Cutaneous Lymphoma (ISCL)/European Organization of Research and Treatment of Cancer (EORTC) revision of classification together with the expected 5-year disease specific survival (DSS) in percent [6–9]

	T	N	M	B	5-year Disease Specific Survival (DSS) (%)
IA	1	0	0	0.1	98
IB	2	0	0	0.1	89
IIA	1.2	1.2	0	0.1	89
IIB	3	0–2	0	0.1	56
IIIA	4	0–2	0	0	54
IIIB	4	0–2	0	1	48
IVA1	1–4	0–2	0	2	41
IVA2	1–4	3	0	0–2	23
IVB	1–4	0–3	1	0–2	18

DSS Disease Specific Survival, *T* Tumor, *N* Lymph node involvement, *M* Metastasis, *B* Blood involvement

vironment might shift from a Th1 to a Th2 phenotype due to an increase in Th2 cytokines and a concomitant decrease in CD8+ T cells, natural killer cells and interferons, which would lead to disease progression [18].

Treatment of CTCL

Treatment of CTCLs is completely different from the treatment of CBCLs. Treatment for MF is always recommended to be stage appropriate, which is a skin-directed therapy in early stage MF (IA–IIA) and systemic therapy for advanced stages (IIB–IVB) [3, 8–10, 19].

Table 3 gives an overview of the various treatment modalities in the respective stages of MF [19].

Skin-directed therapies available in Austria include topical steroids, topical chlormethine, phototherapy and radiotherapy. Phototherapy can be combined with other systemic treatments such as retinoids or

Table 3 Therapy recommendations for MF. (Modified from Dippel [19])

Stages	Recommended first-line therapy	Second-line therapies	
I A	Topical steroids class III, IV PUVA NB-UVB 311 nm Chlormethine hydrochloride 0.02% gel (if available)	Topical bexarotene gel (if available) Topical immunotherapy (imiquimod)	
Localized MF	Topical radiotherapy (RT) (30–36 Gy or 2 × 4 Gy)	Topical steroids class III, IV	–
I B–II A	PUVA NB-UVB 311 nm	PUVA + IFNα PUVA + bexarotene Bexarotene or acitretin Low-dose methotrexate (MTX) Topical RT (8–12 Gy) Mogamulizumab Brentuximab vedotin	–
II B	PUVA ± combined with IFNα, ± oral Bexarotene + RT for tumors	Low-dose methotrexate (MTX) RT for tumors Gemcitabine Doxorubicin/PEGylated Doxorubicin Low dose-electron beam therapy (8–12 Gy) Brentuximab vedotin Pralatrexate Mogamulizumab Allogenic stem cell transplantation	–
III (Erythroderma)	PUVA/NB-UVB ± IFNα, bexarotene Extracorporeal photopheresis ± IFNα, MTX, bexarotene or PUVA	See stage II B Alemtuzumab Chlorambucil/steroid combined	–
IV A	PUVA, ± IFNα, bexarotene, RT for tumors	See stage II B	–
IV B	PUVA, ± IFNα, bexarotene RT for tumors	CHOP/CHOP-like-polychemotherapy Alemtuzumab Cladribine, fludarabine, Cyclophosphamide	–

Acitretin can be used as an alternative drug if bexarotene is contraindicated or intolerable; the order in the table does not represent any ranking. Neither vorinostat (a histone-deacetylase inhibitor) nor pralatrexate were approved in Europe as therapeutic response was insufficient to establish the benefits according to the European Medicines Agency data evidence

PUVA Psoralen Ultraviolet A Therapy, *NB-UVB* Narrow Band Ultraviolet B Therapy, *Gy* Gray, *IFN*α Interferon alpha, *RT* radiotherapy, *MTX* Methotrexate, *CHOP* Cyclophosphamid Doxorubicin hydrochloride Vincristine sulfate Prednisone

IFNα [20]. Local radiotherapy is recommended for MF tumors. Bexarotene, which binds specifically to the retinoid receptor X, is approved for the treatment of CTCL in skin tumor stage (IIB) [21]. Low-dose methotrexate (MTX, 10–25 mg/week) has been used either as monotherapy or also in combination with bexarotene and/or IFNα [19–21]. In advanced stages with visceral involvement, intravenous chemotherapy either as monotherapy with gemcitabine or pegylated liposomal doxorubicin has shown response rates of 67–75% (gemcitabine) or 41–88% (liposomal doxorubicin) [22, 23]. Polychemotherapy did not show added benefit in the response rates, but substantial unfavorable side effects [11, 19–23].

New antibodies have shown beneficial therapeutic effects in recent phase III trials in patients with CTCL:

- Brentuximab vedotin, an anti CD30 IgG1 antibody conjugated to an antimitotic agent named monomethylauristatin E, has reported response rates between 55–70% in patients with CD30-positive CTCL [24]. The antibody showed significantly improved objective response rates and progression-free survival (PFS), compared with either methotrexate or bexarotene (physician's choice) [24].
- Mogamulizumab, an antibody that targets the CC chemokine receptor 4 (CCR4), was approved in 2018 for the treatment of recurrent, progressive or refractory MF/SS. In the phase III MAVORIC trial, mogamulizumab demonstrated superiority to vorinostat in median progression free survival (PFS) and overall response rate (ORR) and a better response in SS patients, according to subgroup analysis [25].
- Alemtuzumab is a monoclonal anti-CD52 antibody; it is not approved for the treatment of cutaneous lymphomas, but has been used more than 10 years ago for the treatment of chronic lymphatic leukemia [26]. In patients with erythroderma and blood involvement it might be a beneficial treatment option [26].

Extracorporeal photopheresis is a leukapheresis-based treatment that has been used for decades for treating erythrodermic MF and SS [19]. Total response rates of about 60% have been reported and combination therapies with retinoids, phototherapy and/or IFNα are common [20].

Cutaneous B cell lymphomas

About 25–30% of primary cutaneous lymphomas are B cell lymphomas (PCBCLs) (Table 1) and three main subtypes have been recognized. The most frequent ones are the primary cutaneous follicle center lymphoma (PCFCL) and the primary cutaneous marginal zone lymphoma (PCMZL), both of which show an excellent 5-year survival rate of 95–99% [2, 27].

The primary cutaneous large B cell lymphoma leg type (PCLBC-LT) is a rare but aggressive lymphoma with a poor outcome [27]. Fig. 2 shows the common skin involvement of the three subtypes. The erythematocyanotic nodules of the PCLBC-LT are very often located on the legs and most common in older woman [2, 27–29]. The 5-year DSS is less than 50% [2, 27–29].

The last classification in the 5th edition of the WHO classification of hematolymphoid tumors [7] did again confirm the less common provisional entities, such as the intravascular large B-cell lymphoma and the Epstein–Barr virus positive (EBV+) mucocutaneous ulcer [7].

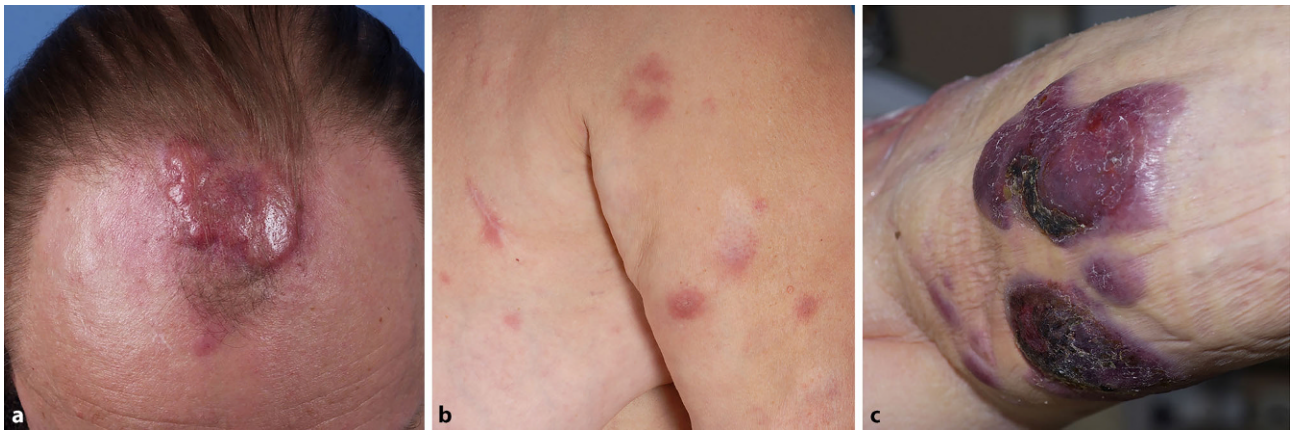

Fig. 2 **a–c** Typical clinical pictures of the three main subtypes of primary cutaneous B cell lymphomas with a follicle center lymphoma (**a**), a cutaneous marginal zone lymphoma (**b**) and a primary cutaneous large B cell lymphoma leg type (**c**). The locations are typical for the respective subtypes

The primary cutaneous follicle center lymphoma (PCFCL) shows a favorable clinical course with an excellent 5-year DSS of 95–99% [2, 27]. Lesions can be solitary or grouped erythematous papules and nodules; the preferential location is the head-neck and trunk area [27, 28]. A typical example is shown in Fig. 2a. Without treatment, lesions may remain stable or enlarge slowly. Transformation into diffuse large B cell lymphoma represents a negative prognostic factor [2, 7, 27–29].

The primary cutaneous marginal zone lymphoma (PCMZL) was recently re-defined as primary cutaneous marginal zone lymphoproliferative disorder [30]. It is preferentially located on the trunk, the arms and occasionally the head with indolent reddish small nodules or papules (Fig. 2b). Although an etiological link with *Borrelia Burgdorferi* has been proposed in European patients, several studies could not show a real correlation [2, 27–29]. According to the consensus classification, it is classified now as a distinct lymphoproliferative entity/disorder and should be segregated from other mucosa-associated lymphoid tissue lymphomas [30].

Due to the lack of randomized controlled trials, treatment recommendations for PCBCLs are largely based on small retrospective studies and institutional experience. Although the indolent forms are characterized by an excellent prognosis, the incidence of relapses is high, varying between 25–68% [27–29]. Apart from radiotherapy and surgical excision, for solitary lesions, therapeutic options include systemic corticosteroids, interferon-α, systemic rituximab and chemotherapy [27–29]. For generalized skin lesions, systemic administration of rituximab is an effective treatment. [27–29]. Treatment for PCLBC-LT is in most cases Rituximab-CHOP [29].

Conclusions

The rare occurrence of primary cutaneous lymphomas emphasizes their special position within the hematolymphoid neoplasms, which is also reflected in the current classification and staging systems. Their treatment might require close interdisciplinary communication and cooperation among specialists in this field.

Although primary cutaneous T and B cell lymphomas are completely different entities, with different clinical pictures and therapies, they share a common feature—the usually benign course in the majority of patients and the restraint of overtreatment.

Take Home Message

The treatment of mycosis fungoides should be stage-adapted and based on an individual approach. A possible maintenance therapy in patients at higher risk for progression/recurrence (≥ stage IIB) is recommended.

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Conflict of interest S. Porkert and J. Valencak declare that they have no competing interests.

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