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Mycosis fungoides and Sézary syndrome

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Mycosis fungoides and Sézary syndrome are primary cutaneous T-cell lymphomas and are rare diseases.

Summary

Mycosis fungoides (MF) and Sézary syndrome (SS) are primary cutaneous T-cell lymphomas (CTCL) with not yet fully understood etiology and pathogenesis. Conceptually, MF and SS are classified as distinct entities arising from different T helper cell subsets. MF is the most common CTCL entity, while SS is very rare. MF presents clinically with patch, plaque and/or tumor stages, but can also evolve as erythroderma, which in turn is pathognomonic for SS. SS is characterized by a detectable tumor-cell burden (Sézary cells) in the peripheral blood consistent with advanced-stage disease and a poor prognosis. In early-stage disease of MF, which is the predominant form, the prognosis is generally favorable. However, in up to 30 % of patients, there is progression of skin lesions, which can ultimately lead to visceral involvement. The histological manifestation of MF can be subtle in early-stage disease and therefore a careful clinicopathological correlation is paramount. The treatment of MF/SS is dependent on the disease stage. Therapeutic options include both skin-directed and systemic regimens. Apart from allogeneic stem cell transplantation (alloSCT), there is as yet no curative therapy for MF/SS. Accordingly, the treatment approach is symptom oriented and aims to reduce the tumor burden and improve health-related quality of life. However, the therapeutic landscape for CTCL is constantly being expanded by the discovery of novel therapeutic targets.

Introduction and epidemiology

Primary cutaneous lymphomas are extranodal non-Hodgkin lymphomas (NHL) and constitute a heterogeneous group of lymphoproliferative diseases with clonal origin from T cells or B cells. Mycosis fungoides (MF) and Sézary syndrome (SS) have been classified as separate entities within the primary cutaneous T-cell lymphomas (CTCL) [1]. Since 1975, the cognisance that neoplastic T cells share not only the same morphology (cerebriform nucleus) but also a common "T-cell phenotype" has been essential for understanding this group of diseases [2, 3]. By definition, CTCL primarily originate from the expansion of clonal T lymphocytes in the skin and are in most cases limited to this organ. However, up to 30 % of patients will experience skin disease progression that can ultimately lead to extracutaneous manifestations [4]. On the other hand, nodal or other extranodal lymphomas may also disseminate into the skin. Such lesions are defined as secondary cutaneous lymphomas [5]. Both the clinical appearance and the histology of some cutaneous lymphomas may show morphological similarities to nodal lymphomas with secondary skin involvement, but there are clear differences as to prognosis and therapeutic options. Separate classification thus remains necessary [1, 6].

CTCL are rare diseases (*orphan diseases*; ORPHA: 171901), and also rare tumors. After the gastrointestinal MALT lymphomas, though they constitute the second most frequent group of extranodal NHL [7]. CTCL patients experience significant impairment of their health-related quality of life (HRQoL), due to the

cancer diagnosis itself and the visible stigma of skin lesions with often agonizing pruritus [8–11].

The peak of diagnosis is between 55 and 60 years of age, with male preponderance (m : w = 2 : 1) [12]. CTCL constitute 83 % of all cutaneous lymphomas. Regional differences have been reported, with a 15–17 % higher frequency in Asia and South America as compared to Europe [13]. The incidence of all cutaneous lymphomas has been reported to be about 0.64–0.87/100 000 per year for the USA [14–19], and 0.29–0.39/100 000 in Europe [20–23]. Current registry data from France, however, show an incidence of 0.96/100 000 for cutaneous lymphomas, which is near the incidence in the USA [24]. The joint Dutch and Austrian cutaneous lymphoma registry reports MF as the most common entity of CTCL with a frequency of about 39%, while SS is a very rare variant with a frequency of only 2% [5]. Future variations of the incidence rates of subtypes can be attributed to improved diagnostics and classification [24].

Mycosis fungoides is the most common form of cutaneous lymphoma, accounting for approximately 39 %. Sézary syndrome is much less common, at about 2 %.

Classification

The WHO-EORTC classification of cutaneous T-cell lymphomas is based on clinical, histological, immunohistological, and molecular biological criteria, and is essential for the classification and exact diagnosis of cutaneous lymphomas.

The introduction of the original umbrella term "CTCL" in 1975 led to the disadvantage that subsequent publications often did not clearly distinguish between subtypes regarding clinical presentation and prognosis. At the same time, the classifications used for lymphomas back then (WHO 1976, Kiel 1988, REAL 1994) proved to be completely unsuitable for cutaneous lymphomas [2]. The publication of the common WHO-EORTC classification for cutaneous T-cell and B-cell lymphomas in 2005 was indeed the start of a new era [1]. It became possible to distinguish between CTCL subtypes based on clinical, histological, immunohistological, and molecular criteria, and even achieve a basic classification with regard to prognosis.

An update was incorporated in the WHO classification in 2008, and another updated version with small revisions was published in 2016 [7]. The current classification for cutaneous lymphomas, WHO-EORTC 2018 [5], is an updated version of the original gold standard published in 2005 [1]. Combined assessment of clinical presentation and histopathology (clinicopathological correlation, CPC) is essential for the classification and exact diagnosis of cutaneous lymphomas. Examples include acral $CD8^+$ T-cell lymphoma, aggressive epidermotropic $CD8^+$ CTCL, and $CD8^+$ MF as these can only be distinguished in correlation with the clinical presentation [5]. It should be mentioned that $CD8^+$ MF is actually not listed as a distinct MF variant [25]. Table 1 shows the current classification of CTCL, including MF and SS, according to the updated WHO-EORTC classification 2018. This classification allows a differentiation of about 95 % of all cutaneous lymphomas [5].

Etiology and pathogenesis

The etiology of mycosis fungoides and Sézary syndrome is still unclear and is currently under intense scientific research.

The etiology of CTCL is largely unknown. Infectious agents, ultraviolet (UV) radiation, or occupational exposure are being discussed as possible triggers [26–30].

There does not appear to be a familial accumulation [31]. There is evidence of genomic alterations in putative oncogenes and tumor suppressor genes, including NF-κB and the Jak-STAT pathway, though with significant heterogeneity between patients [32–39]. An integrated genomic database of CTCL showed exclusive and individual mutations that influence p53 or NF-κB/KIT genes and pathways. In cases without p53 or NFκ-B/KIT anomalies, other aberrant genomic characteristics influencing transcription and epigenetic regulation (resulting in mutation) were

Table 1 Classification of CTCL adapted from the WHO-EORTC classification of cutaneous T-cell lymphomas (update 2018) [5].

	Frequency (%)	Disease-specific five-year survival (%)
Mycosis fungoides (MF)	39	88
Mycosis fungoides variants		
– Folliculotropic MF	5	75
– Pagetoid reticulosis	< 1	100
– Granulomatous slack skin	< 1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	< 1	NDA
Primary cutaneous CD30-positive lymphoproliferative diseases		
– Primary cutaneous anaplastic large-cell lymphoma	8	95
– Lymphomatoid papulosis	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	< 1	16
Chronic active EBV infection	< 1	NDA
Primary cutaneous peripheral T-cell lymphomas, rare subtypes		
– Primary cutaneous γ/δ T-cell lymphoma	< 1	11
– Primary cutaneous CD8-positive epidermotropic aggressive T-cell lymphoma (preliminary)	< 1	31
– Primary cutaneous CD4-positive small to medium cell lymphoproliferation (preliminary)	6	100
– Primary cutaneous acral CD8-positive T-cell lymphoma (preliminary)	< 1	100
Primary cutaneous peripheral T-cell lymphomas, NOS	2	15

Abbr.: EBV, Epstein-Barr virus; NDA, no data available; NK, natural killer cells; NOS, not otherwise specified.
Listed here are only CTCL, with partially modified terminology, new provisional entities and an update regarding incidence and 5-year survival rate. Both the frequency and the prognosis were determined based on the joint Dutch and Austrian registry for cutaneous lymphomas.

Mycosis fungoides and Sézary syndrome originate from different T-cell types. Thus, the two diseases constitute different entities.

detected [40]. Epigenetic modification (pathological gene methylation and histone deacetylation) as well as dysfunctional regulation of cytokines and other signaling molecules are thought to play a decisive role in the malignant transformation of CTCL [32, 41, 42]. MF tumor cells have been identified as skin-resident $CD4^+$ effector memory T cells of clonal origin. They are part of the local cutaneous immune response [43]. These cells are long-lived and stay in their "home tissue" – which may explain the fact that MF remains limited to the skin for many years or even decades. In contrast, SS cells have been classified as central memory T cells with expression of the lymph node homing molecules CCR7 and L-selectin [43, 44]. These cells circulate between the skin, lymph nodes, and blood, and are important for the communication between these compartments. Sézary cells infiltrate the skin in a diffuse manner, which is clinically reflected as erythroderma. Those cells are also more often and easier detected in the blood and lymph nodes [44, 45].

CTCL cells express cytokines from various T helper cell subtypes, including T helper 2 (Th2), Th17, and regulatory T cells [46–49]. According to recent evidence, in early MF the tumor micromilieu mainly consists of benign Th1 cells, regulatory T cells, and cytotoxic $CD8^+$ T cells (tumor infiltrating lymphocytes or TILs),

which appear to control the malignant T cells, at least initially. In cases of disease progression, a shift from benign "bystander" infiltration with a Th1 phenotype towards a preponderance of the Th2 phenotype including blood eosinophilia and increased IgE has been reported [32]. Reversal of this shift (from Th2 to Th1) has been demonstrated, independently of tumor cell burden, after successful treatment of MF lesions, such as with PUVA *in vivo* (psoralen plus UVA therapy), and after checkpoint blockade *in vitro* [50, 51]. The Th1 immune signature is traditionally considered to be protective in early stages (due to the accompanying "anti-tumor" infiltration), while its gradual loss with increase of Th2 mediators is ascribed to disease progression [49]. Here, Th2 cytokines are thought to suppress proliferation of benign T cells and inhibit maturation of dendritic cells (DC) [49, 52, 53]. Immature DC can induce tolerance by presenting antigens to T cells without appropriate co-stimulation, thus promoting a tumor-tolerant (micro-)environment [54]. Correspondingly, increased numbers of immature DC have been observed in MF lesions. This may constitute an important mechanism for tolerance towards malignant T cells [55, 56]. Current data also indicate that skin colonization with *Staphylococcus aureus* in MF patients (a common complication) may actually promote disease progression via positive selection of $CD4^+$ tumor cells by staphylococcal alpha-toxin [57].

Clinical presentation: Mycosis fungoides versus Sézary syndrome

MF clinically presents with stages from patches to plaques, and tumors. These stages may co-exist and individual stages may be skipped. Patches are defined as erythematous macules with varying desquamation and size. They can be either localized or generalized mainly in skin areas without sun exposure (Figure 1). Although patches are usually considered a clinical sign of early disease, they may also occur in advanced-stage MF (Figure 2), or during recurrence after successful treatment of plaques or tumors. In contrast, plaques are infiltrated, erythematous or brownish lesions with irregular margins and varying epidermal involvement (Figure 3). They must be differentiated from flat tumors [58]. Tumors are defined as having a diameter of ≥ 1 cm; they develop from existing patches or plaques (Figure 4a) but may also occur *de novo* (Figure 4b). This variant of MF had previously been

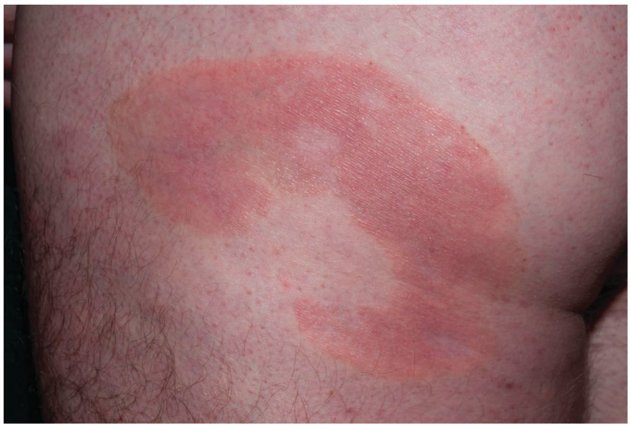

Figure 1 Mycosis fungoides: Patch-stage. Patch.

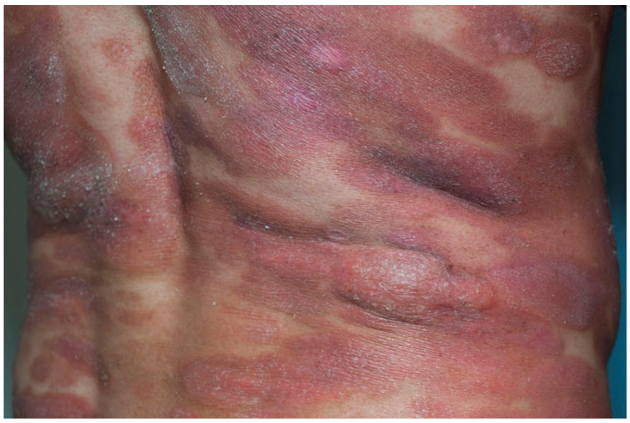

Figure 2 Mycosis fungoides: tumor-stage. Co-existing patches, plaques, and tumors.

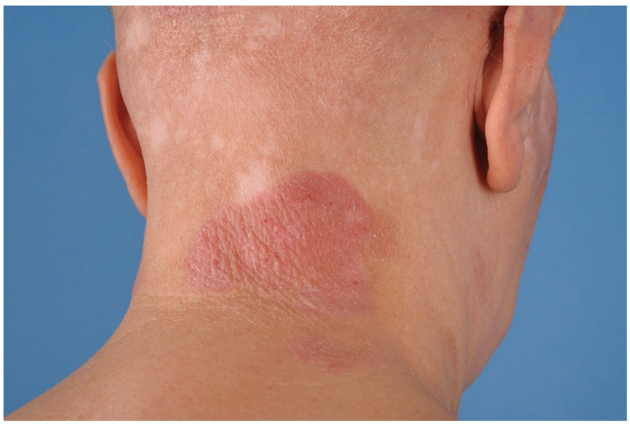

Figure 3 Mycosis fungoides: plaque-stage. Recurrence of a plaque after total skin electron beam therapy.

Mycosis fungoides presents with various clinical stages.

termed "MF *tumour d'emblee*", though improved immunohistochemical and/or molecular diagnostic measures of today might identify some of these cases as non-MF or even B-cell lymphomas [59].

MF tumors tend to ulcerate, but growth may be variable. Rapid growth over a period of a few weeks, relatively stable tumor sizes for months, as well as partial regression of tumors may be observed. Apart from "classic" MF, the following variants have been officially recognized based on clinical and histopathological features: folliculotropic MF (Figure 5), pagetoid reticulosis (Figure 6), and granulomatous slack skin (Figure 7). Hypopigmented MF (Figure 8) is currenlty not yet recognized as an independent disease variant. The two latter entities are very rare, but folliculotropic MF occurs in about 10 % of cases. Clinically, folliculotropic MF presents with characteristic follicular (usually clustered) papules mostly in the head and neck region, as well as acneiform lesions and associated alopecia [60].

Apart from the patch, plaque, and tumor stages, there is a fourth skin stage for MF characterized by erythroderma (erythrodermic MF). This must be differentiated from SS since prognosis and therapeutic recommendations differ [58].

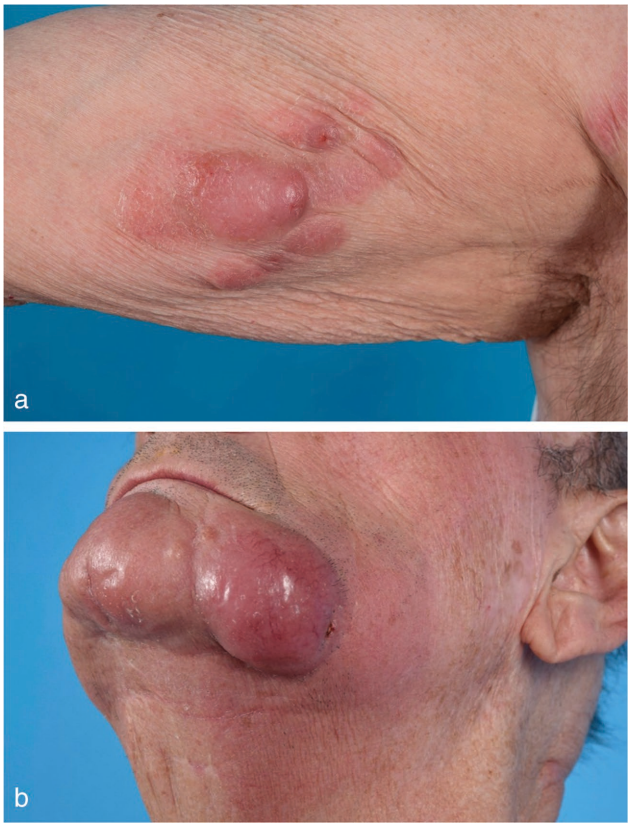

Figure 4 Mycosis fungoides: tumor-stage. Tumors developed in close vicinity to preexisting patches and plaques (a). Mycosis fungoides: tumor-stage, showing a single tumor (b).

The clinical presentation of SS is characterized by the triad of erythroderma (≥ 80 % of the body surface area affected) (Figure 9), lymphadenopathy, and Sézary cells (atypical T cells with cerebriform nuclei) in the skin, lymph nodes, and peripheral blood [61, 62]. A recent study reports the following additional clinical features of SS: palmoplantar hyperkeratoses (37.6 %), onychodystrophy (15.6 %), alopecia (10.9 %), leonine facies (3.6 %), and ectropion (3.4 %) [61].

In addition to circulating Sézary cells, the blood also shows an increased absolute number of $CD4^+$ T lymphocytes resulting in a shifted/increased $CD4^+$:$CD8^+$ ratio. The percentage of $CD4^+/CD7^-$ and $CD4^+/CD26^-$ circulating T cells is determined to assess tumor blood burden, and recently threshold values for absolute tumor cell counts have been discussed – especially for evaluating therapeutic success [63, 64]. Since the clinical presentation and histopathology may sometimes be non-specific, it is essential to evaluate peripheral blood involvement and the medical history in order to differentiate between erythrodermic MF and SS. According to the current classification, at least one of the following criteria must be fulfilled to diagnose SS an absolute Sézary cell count of > 1000/µl or an increased $CD4^+$ T-cell population, a $CD4^+/CD8^+$ ratio ≥ 10, $CD4^+/CD7^-$ cells ≥ 40 % or $CD4^+/CD26^-$ cells ≥ 30 %. Recent studies have described new biomarkers such as PD-1 (CD279), KIR3DL2 (CD158k), T-plastin and Twist. These should facilitate differentiation between SS and benign erythrodermic dermatoses both in the skin and peripheral blood [5, 64].

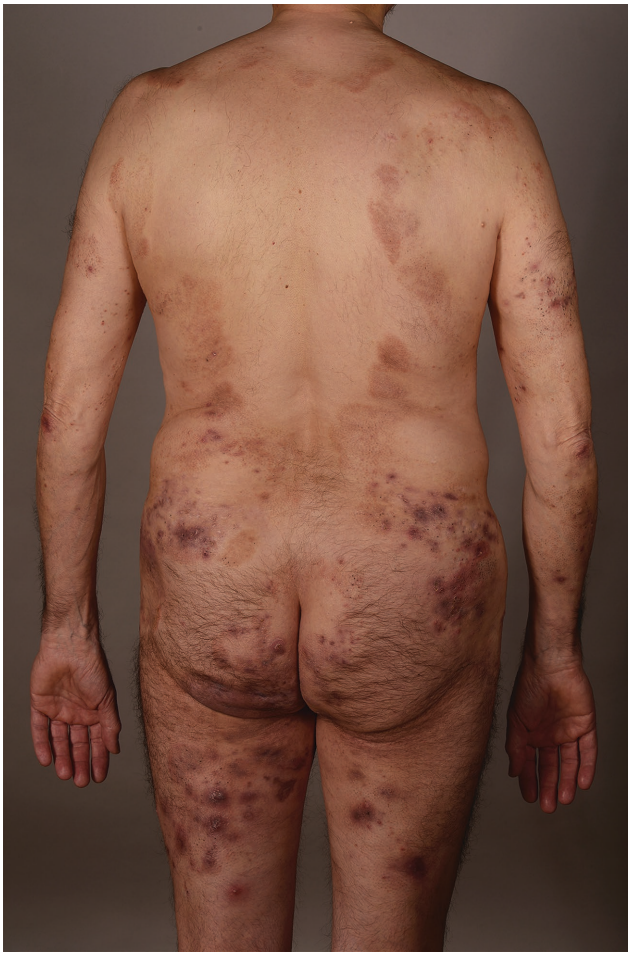

Figure 5 Folliculotropic mycosis fungoides: erythematous plaques with follicular accentuation and hair loss, combined with comedones and solitary, follicular erythematous papules.

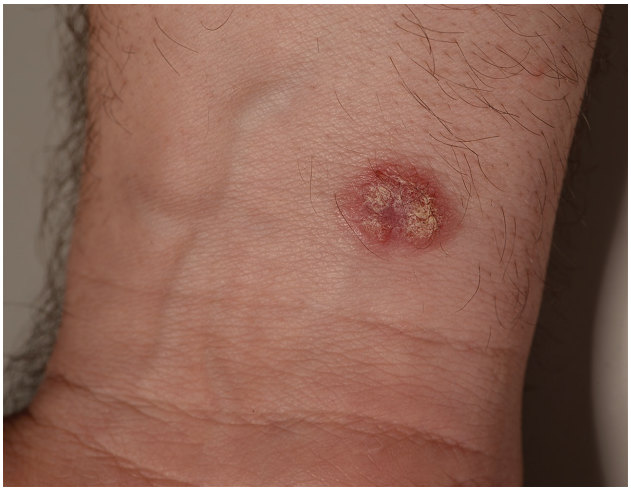

Figure 6 Mycosis fungoides variant: pagetoid reticulosis. Solitary scaly plaque located on the ventral forearm.

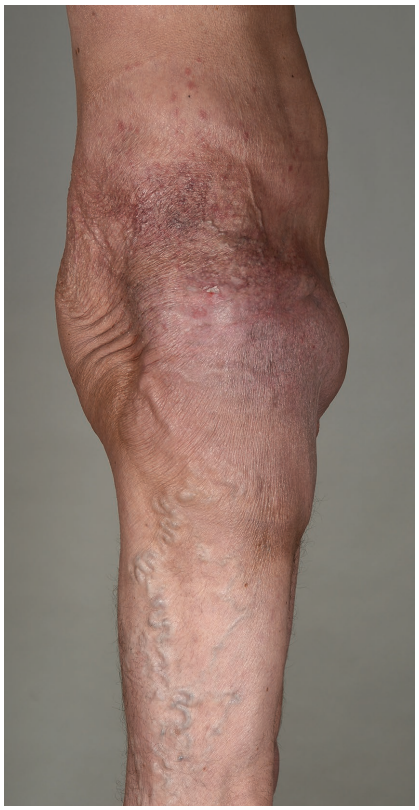

Figure 7 Mycosis fungoides variant: granulomatous slack skin. Large, slack, partially pendulous, erythematous-violaceous plaque in the right inguinal region, extending over the right hip and buttock.

Differential diagnoses for Mycosis fungoides and Sézary syndrome

Differentiating between mycosis fungoides/Sézary syndrome and inflammatory dermatoses can be challenging.

Early stage MF must be differentiated from small-patch parapsoriasis, microbial or atopic eczema, psoriasis vulgaris, and pityriasis rosea. In the plaque stage of MF, differential diagnoses include pseudolymphoma of the skin, leukemia of the skin, lupus erythematosus tumidus, urticaria pigmentosa, and tinea corporis. MF in the tumor stage must be differentiated from other cutaneous T-cell lymphomas as well as cutaneous B-cell lymphomas [65]. Other, non-neoplastic differential diagnoses of SS include psoriatic erythroderma, atopic dermatitis, pityriasis rubra pilaris, and drug rashes. Differentiating between MF/SS and inflammatory dermatoses can be challenging [66, 67].

Histopathology: Mycosis fungoides versus SS

In early stages of mycosis fungoides, histopathological diagnosis is often difficult and relies on clinicopathological correlation.

Especially in early stages, histopathological diagnosis of MF is often difficult in spite of clearly defined criteria. It usually requires meticulous correlation with the clinical presentation [68, 69].

In cases of morphologically different clinical lesions, multilateral biopsies are recommended. Any specific topical treatments (such as topical corticosteroids)

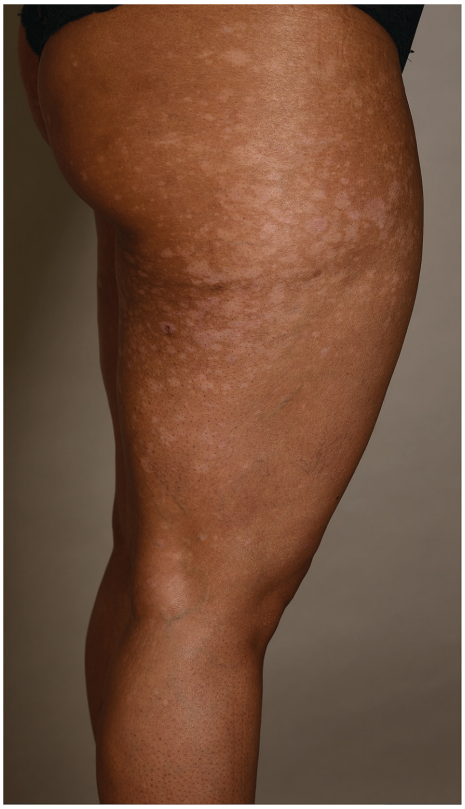

Figure 8 Hypopigmented mycosis fungoides: partly confluent, partly solitary hypopigmented patches.

must be discontinued about two weeks in advance. Repeat biopsies should always be performed in cases of recurrence and/or lesions with altered morphology, so changes can be detected early (for example large-cell transformation, for therapeutic option of brentuximab vedotin if CD30 positive) [70]. In the patch stage of early MF, infiltrates contain mostly small lymphocytes with only a small number of atypical cells. In this case, epidermotropism of individual lymphocytes is usually considered "disproportionate epidermotropism", signifying the presence of several intraepidermal, usually solitary lymphocytes without pronounced epidermal spongiosis. Conversely, intraepidermal lymphocytes may also be found in eczema, but in these cases they will occur in distinctly spongiotic areas. In MF, intraepidermal lymphocytes often show a halo nucleus. Pautrier's micro-abscesses are intraepidermal clusters of numerous lymphocytes. They are considered a diagnostic clue; however, they are rare in early MF. Other diagnostic indications include solitary epidermotropic lymphocytes as well as lymphocytes lined up along the basement membrane in a "string-of-pearls" pattern (basal epidermotropism or "lining up" phenomenon) (Figure 10) [58, 71]. In about 5 % of early MF cases, no epidermotropism can be detected. Lymphocytic infiltrations in the dermis are either patchy-lichenoid or band-like. The papillary dermis may show mild fibrosis and/or coarse collagen fiber bundles with wire-like thickening („wiry bundles of collagen") (Figure 10).

The classic histological findings during the patch or plaque stages (Figure 11a) show a dense band-like infiltration in the upper dermis, consisting of small or medium-sized lymphocytes, some of which may have a larger, pleomorphic

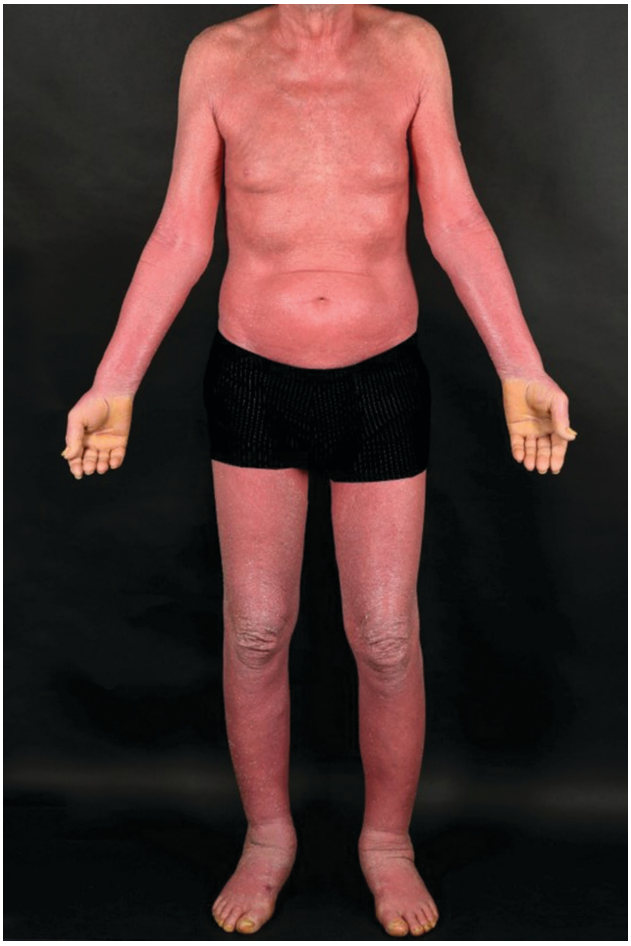

Figure 9 SS erythroderma und palmo-plantar hyperkeratosis.

nucleus. Pronounced epidermotropism with Pautrier's micro-abscesses is typical (Figure 11b). The epidermis is frequently acanthotic, with parakeratosis. During the tumor stage (Figure 12a), dense, diffuse or nodular infiltrations of lymphocytic cells can be detected in the dermis, and the subcutaneous fat may also be affected. Eosinophilic granulocytes as well as histiocytes accumulate with varying density [58]. High mitotic activity is typical, and solitary blastic tumor cells can be found. Epidermotropism may sometimes be lost during this stage, but in many cases pronounced epidermotropism with Pautrier's micro-abscesses is still present. The epidermis shows either acanthosis with parakeratosis, or atrophy. Follicles are frequently destroyed. Large-cell transformation (LCT) is considered a histological criterion and is defined by large lymphocytes constituting more than 25 % of the infiltration (Figure 12b) or accumulating in nodular aggregations. LCT may be either $CD30^+$ or $CD30^-$ and is mainly observed during the tumor stage. However, accumulation of large lymphocytes is sometimes detected in plaques and more rarely even in patches [58].

The histopathological signs of SS are similar to MF. The two entities cannot be distinguished with certainty on the basis of dermatopathology only. In recently developed SS, epidermotropism is less pronounced, and the histopathological findings are mainly non-specific, with a "pseudo-dermatitis" pattern [72].

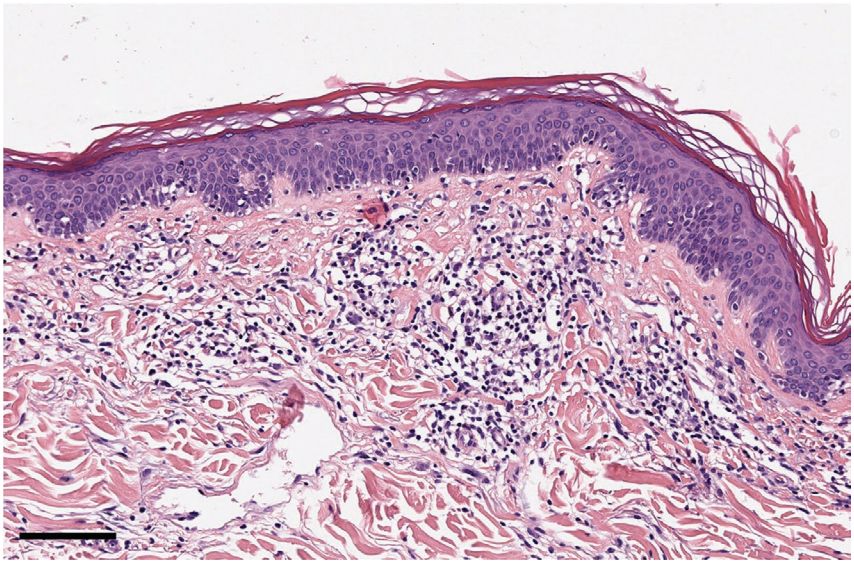

Figure 10 Early mycosis fungoides: lining-up of lymphocytes along the basal layer. Fibrosis of the papillary dermis (hematoxylin eosin stain, scale bar: 200 μm).

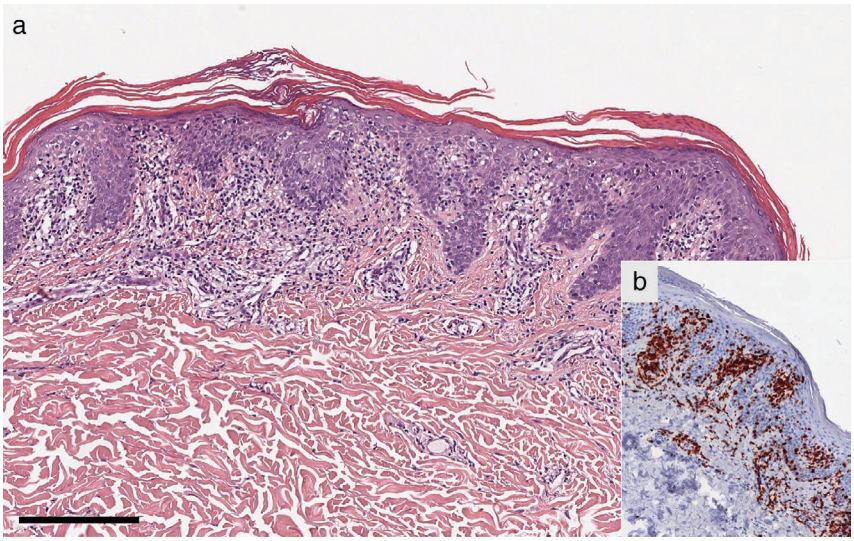

Figure 11 Histopathologic features of clear-cut mycosis fungoides at the patch or plaque stage. Band-like infiltrate of lymphocytes within the superficial dermis and epidermotropism with Pautrier's microabscesses (hematoxylin eosin stain, scale bar: 200 μm) (a). Immunohistochemical staining of CD3 shows Pautrier's microabscesses within the epidermis (b).

Solitary large lymphocytes can be found in many cases, but their diagnostic relevance is unclear since they may also occur in benign inflammatory infiltrates. In advanced-stage disease, dense infiltrations of Sézary cells show numerous cerebriform nuclei (Figure 13). Immunohistochemistry, as well, cannot detect clear differences between SS and MF. Both entities typically show a T helper cell phenotype ($CD3^+$, $CD4^+$, $CD8^-$), and in SS, PD1 is usually strongly positive [51]. CD30-positivity is mainly found in LCT.

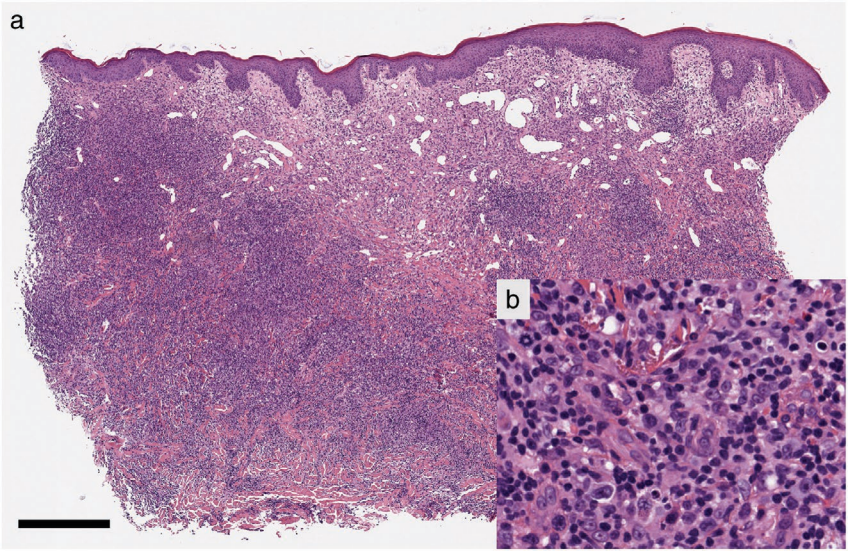

Figure 12 Histopathology in tumors of mycosis fungoides with large cell transformation. Deep, diffuse infiltrates of lymphocytes within the dermis. Loss of epidermotropism. (hematoxylin-eosin stain, scale bar: 500 μm) (a). Magnification of large immunoblastic cells intermingled with medium sized lymphocytes (b).

Diagnostics, staging, and prognosis

It is important not to put too much emphasis on molecular and histological findings as compared with the clinical presentation and medical history, since this might lead to overtreatment.

Diagnostics, staging, and also the subsequent planning of treatment for MF/SS are based on a careful medical history, a meticulously documented examination of the skin lesions, histological investigations (including immune phenotyping

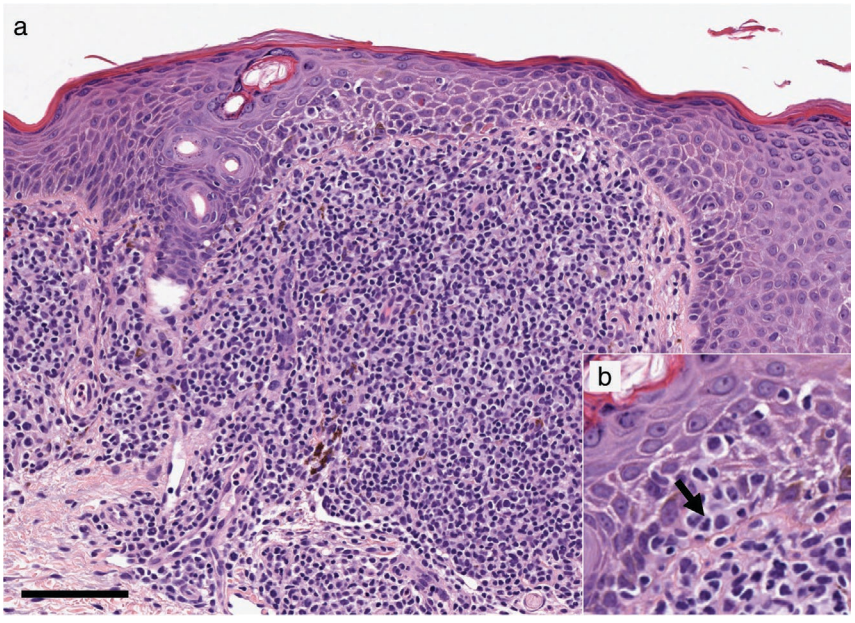

Figure 13 Sézary syndrome. Dense, band-like infiltrate of medium-sized, pleomorphic lymphocytes (hematoxylin-eosin stain, scale bar: 100 μm) (a). Marking of a Sézary cell with a cerebriform nucleus (arrow) (b).

and if appropriate clonality testing), laboratory investigations (including flow cytometry) which in special cases may also include immune phenotyping and/or molecular testing of blood or bone marrow, as well as diagnostic imaging such as lymph node sonography and whole-body CT. It is important not to put too much emphasis on the molecular and histological findings as compared with the clinical presentation and medical history, since this might lead to overtreatment.

Monoclonality, as assessed by TCR rearrangement, for example, may also be found in inflammatory diseases, so detection of this feature is of limited significance for diagnosis and prognosis [73]. The current Sk2 guideline "Cutaneous Lymphomas" published by the German Working Group on Dermatological Oncology (ADO, Arbeitsgemeinschaft Dermatologische Onkologie), the German Cancer Society (DKG, Deutsche Krebsgesellschaft) and the German Dermatological Society (DDG, Deutsche Dermatologische Gesellschaft) recommends the procedure shown in Table 2 for diagnostics and staging of MF and SS [74].

Staging of mycosis fungoides/Sézary syndrome is performed according to the TNMB classification, which includes the primary tumor (T), lymph node involvement (N), organ metastases (M), and the number of tumor cells in the peripheral blood (B).

Staging of MF and SS is based on the revised, internationally established TNM classification published by the International Society of Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC). Apart from the skin findings – primary tumor (T), involvement of lymph nodes (N), and remote metastases (M) – this classification also includes detection of atypical lymphocytes/Sézary cells in peripheral blood (B). It is therefore referred to as the TNMB classification [59] (Table 3).

Involvement of the peripheral blood (number of Sézary cells > 1000/µl) is a diagnostic prerequisite for Sézary syndrome.

The classification identifies four clinical stages of the disease (Table 4). Each of the stages is associated with a specific estimated survival rate (five-year survival) and is thus prognostically relevant since validated (bio)markers are currently lacking (Table 4) [59, 75]. SS with confirmed involvement of the blood (Sézary cells > 1000/µl in the peripheral blood) is therefore at least assigned stage IVA_1.

Factors that aggravate prognosis in mycosis fungoides and Sézary syndrome, apart from the clinical stage, include advanced age, male gender, increased LDH, and large-cell transformation.

As to the few known prognostic factors apart from the clinical stage, a univariate retrospective analysis found that advanced age, male gender, increased levels of lactate dehydrogenase (LDH), and LCT decreased survival and increased the risk of disease progression [76]. Recent data on sex-related differences in MF found that the five-year overall survival was 76.9 % in women versus 70.7 % in men. Estrogen effects on the differentiation of lymphoma cells and the antitumor immune response were discussed as underlying reasons [77].

Conversely, patients with hypopigmented, poikilodermal MF or with MF associated with lymphomatoid papulosis, show better survival rates and a decreased risk of disease progression [75, 78]. A multivariate analysis has also shown that tumor clonality without Sézary cells in the peripheral blood, as well as folliculotropic MF, constitute independent predictors for a poor survival rate and increased risk of disease progression [79]. Folliculotropism, however, has also been associated with a favorable prognosis [80].

Treatment of Mycosis fungoides and Sézary syndrome

Skin-directed treatment options for mycosis fungoides or Sézary syndrome include topical steroids, mechlorethamine, UVB irradiation, PUVA, radiotherapy, and total skin electron beam.

Treatment for both MF and SS is based on guidelines, in Europe usually the EORTC consensus recommendations [81]. All guidelines on the treatment of CTCL agree that in the face of current incurability (despite of allogeneic stem cell transplantation) patients should receive palliative treatment. Skin-directed therapy (SDT) should be administered as a first-line treatment in early stages of the disease, and systemic (more aggressive) therapies should be introduced only after disease progression.

Table 2 Diagnosis and staging examinations for mycosis fungoides and Sézary syndrome modified according to the S2k guideline – Cutaneous lymphomas Update 2016 – Part 1: Classification and diagnostics (ICD10 C82 - C86) [74].

	Investigation	Method/procedure
Medical history	– Duration, type, and extent as well as temporal development of skin lesions	
Clinical examination	– Careful examination of the skin – Lymph node status – Palpation of liver and spleen – B symptoms	Recommendation: use data entry form and photographic documentation
Laboratory investigations	– Differential blood count, electrolytes, liver enzymes, creatinine, lactate dehydrogenase, C-reactive protein, – Immunoelectrophoresis if indicated – Borrelia serology if indicated* – Special hematological investigations if indicated* – Other laboratory investigations as required by the planned treatment	*For erythrodermic T-cell lymphomas:* – Blood smear for detection of Sézary cells – FACS, CD_4/CD8 ratio, assessment of $CD4^+/CD7^-$ cells and/or $CD4^+/CD26^-$ cells – Clonality analysis in the blood (PCR, BIOMED-2 protocol [19]) – Bone marrow biopsies are not indicated for diagnostics.
Biopsy	– Histology, immunohistochemistry, and molecular diagnostics of skin lesions as well as suspicious enlarged lymph nodes, and if indicated also in cases of suspected organ involvement (clonality analysis according to BIOMED-2 protocol if indicated)	*For T-cell lymphomas:* – Molecular investigations with PCR for the T-cell receptor chain (TCR-gamma PCR, BIOMED-2 protocol)
Staging investigations		
Clinical presentation	*Diagnostic imaging*	
Mycosis fungoides	– chest X-ray – abdominal and lymph node ultrasound	
Mycosis-fungoides variants: – Folliculotropic mycosis fungoides – Pagetoid reticulosis – Granulomatous slack skin	– chest X-ray – abdominal and lymph node ultrasound	
Mycosis fungoides stage IIB and above	– Whole-body CT** – Lymph node ultrasound – If indicated: PET-CT***	
Sézary syndrome	– Whole-body CT** – Lymph node ultrasound – If indicated PET-CT***	

Abbr.: FACS *Fluorescence Activated Cell Sorting*; PCR: *Polymerase Chain Reaction*); PET-CT, Positron emission tomography-computed tomography; 18F-FDG, 18 F-fluordesoxyglucose.

*The recommendations apply to first-time staging. Individually adapted investigations should be performed after treatment, in case of disease progression, and yearly in cases of aggressive lymphomas.

**Whole-body CT: CT of the neck, chest, abdomen and pelvic area with intravenous contrast agent.

***Retrospective investigations with small numbers of cases mostly showed clear superiority of 18F-FDG PET/CT as compared with conventional diagnostic imaging, particularly in detecting lymph node and organ involvement. At the present time, large prospective studies with sufficient evidence are lacking. As a rule, costs for PET-CT investigations for this indication are not covered by statutory health insurance companies in Germany.

Table 3 TNMB-classification of mycosis fungoides and Sézary syndrome according to the revision of the ISCL/EORTC [59].

TNMB stage	Descriptions
Skin (T)	
T1	Macules, papules and/or plaques (≤ 10 % of the skin surface area)
T1a	Only macules
T1b	Plaques ± macules
T2	Macules, papules, or plaques (≥ 10 % of the skin surface area)
T2a	Only macules
T2b	Plaques ± macules
T3	≥ 1 tumors (diameter ≥ 1 cm)
T4	Erythroderma (≥ 80 % of the skin surface area)
Lymph nodes (N)	
N0	No palpable peripheral lymph nodes
N1	Palpable lymph nodes, no histological evidence of CTCL ($NCILN_{0–2}$)
N1a	Clone negative
N1b	Clone positive
N2	Palpable lymph nodes, histology shows sparse T-cell lymphoma infiltrations ($NCILN_3$)
N2a	Clone negative
N2b	Clone positive
N3	Palpable lymph nodes, histology shows extensive T-cell lymphoma infiltrations ($NCILN_4$), clone positive or negative
Visceral/metastases	
M0	No involvement of visceral organs
M1	Visceral involvement (with histological evidence and specification of the organs involved)
Peripheral blood (B)	
B0	No significant involvement of the blood (< 5 % atypical lymphocytes/Sézary cells)
B0a	Clone negative
B0b	Clone positive
B1	Atypical lymphocytes in the peripheral blood (≤ 5 %)
B1a	Clone negative
B1b	Clone positive
B2	Sézary cells > 1000/l or increased $CD4^+$-T-cell population, $CD4^+/CD8^+$ ratio ≥ 10, $CD4^+/CD7^-$ cells ≥ 40 % or $CD4^+/CD26^-$ cells ≥ 30 %

An exact diagnosis with detailed staging is the prerequisite for adequate therapeutic management. Individual treatment depends not only on staging but also on previous therapies. Patients' preferences and HRQoL, as well as availability and expertise are important considerations [82].

The various therapeutic approaches available in Europe are described below. Recommendations for the use of the respective treatment modalities according to

Table 4 Clinical stages of mycosis fungoides and Sézary syndrome and the respective prognosis and the disease-specific 5-year survival rate [59].

Stage	T	N	M	B	Prognosis: 5-year survival rate (%)
IA	1	0	0	0 or 1	98
IB	2	0	0	0 or 1	89
IIA	1 or 2	1 or 2	0	0 or 1	89
IIB	3	0–2	0	0 or 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 or 2	23
IVB	1–4	0–3	1	0 or 2	18

clinical stage (stage-appropriate therapy) and indication (MF or SS) are listed in Tables 5 (MF) and 6 (SS).

Skin-directed therapies

The SDT available in Europe include topical corticosteroids, topical mechlorethamine (chlormethine), phototherapy, and radiotherapy. Topical corticosteroids are mainly recommended for localized lesions in the patch and plaque stages. As for the evidence level, an overall response rate of 94 % with twice daily use has been shown in a single study, with 85 % of patients receiving a class IV steroid [83]. Topical mechlorethamine gel (0.016 %) is approved in Europe as a first-line treatment for all stages of the disease. The EORTC consensus also recommends mechlorethamine as maintenance therapy after remission has been achieved, with an evidence level of II [82, 84]. The pivotal study showed a total response rate of 58.5 % after six months of once-daily application, with index lesions responding after about 26 weeks. Burning, pruritus, and contact dermatitis occurred in 50 % of cases and resulted in discontinuation of this treatment in 20 % [85]. Narrow-band UVB (NB-UVB) is used for MF patients in the patch stage (T1a undT2a), and 8-methoxypsoralen plus UVA (PUVA) in the plaque stage, due to better dermal penetration. Phototherapy can be combined with other systemic treatments such as retinoids or interferon alpha (IFNα) [82]. Since MF tumor cells is particularly sensitive to radiation, local radiotherapy is recommended as an effective palliative treatment option for solitary thick plaques or tumors, but also for unilesional MF/pagetoid reticulosis [86, 87]. Total skin electron beam (TSEB) irradiation at a standard dose of 30–36 Gy over a period of 8–10 weeks gave complete remission (CR) rates of 47 % in T2 and 75 % in T3, and also a decreased peripheral tumor cell burden in SS [88]. Recent data on the efficacy of low-dose TSEB with 12 Gy showed a total response rate of 88 % with 24 % CR, no toxicity above grade III, and a significant improvement of HRQoL with decreased disease burden [89].

Table 5 EORTC recommendations for the treatment of mycosis fungoides [82].

Mycosis fungoides	First-line treatment	Second-line treatment
IA–IIA	– Watch and wait (particularly IA) – Topical corticosteroids (particularly T1a and T2a) – Topical mechlorethamine (IA/IB) – UVB – PUVA – Localized radiotherapy (unilesional MF/pagetoid reticulosis)	– Retinoids/IFNα2b – TSEB (particularly T2b) – Low-dose MTX
IIB	– Retinoids/IFNα2b – TSEB – Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine) – Low-dose MTX – Localized radiotherapy	– Polychemotherapy (CHOP/CHOP-like chemotherapy) – Allogeneic stem cell transplant
IIIA and IIIB	– Retinoids/IFNα2b – ECP, in combination as indicated – Low-dose MTX – TSEB	– Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine) – Allogeneic stem cell transplant
IVA and IVB	– Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP, CHOP-like chemotherapy) – Radiotherapy (localized, TSEB) – Alemtuzumab (particularly B2) – Allogeneic stem cell transplant	

Abbr.: CHOP, chemotherapy with cyclophosphamide, hydroxydaunomycin, vincristine, prednisolone; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MTX, methotrexate; PUVA, psoralen plus UVA-irradiation; TSEB, total skin electron beam; UVB, UVB-phototherapy.

Systemic treatment

Systemic treatment options for mycosis fungoides or Sézary syndrome include extracorporeal photopheresis, IFNα2b, retinoids, chemotherapies, and antibodies.

The systemic treatment options available in Europe include extracorporeal photo pheresis (ECP), retinoids/rexinoid, IFNα2b, as well as chemotherapies and antibody treatments. Retinoids (acitretin and isotretinoin) are vitamin A derivatives. They

Table 6 EORTC recommendations for the treatment of Sézary syndrome [82].

Sézary syndrome	First-Line treatment	Second-Line treatment
IVA1–IVB	– ECP – Chlorambucil and corticosteroids – ECP/PUVA + Retinoids/IFNα2b – Low-dose MTX	– Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP, CHOP-like chemotherapy) – Alemtuzumab – Allogeneic stem cell transplant

Abbr.: CHOP, chemotherapy with cyclophosphamide, hydroxydaunomycin, vincristine, prednisolone; ECP, extracorporeal photopheresis; IFNα2b, interferon alpha; MTX, methotrexate; PUVA, psoralen plus UVA-irradiation.

have been successfully used for treating CTCL as monotherapy or in combination but are not approved for this indication [82]. However, bexarotene, which specifically binds to the retinoid-X receptor (rexinoid), is approved for treating CTCL in the skin tumor stage (stage IIB) if the disease has been refractory to at least one systemic therapy [90]. Previously, only recombinant IFNα2b was approved for treating MF/SS. Since this is currently no longer available, pegylated IFNα2b is now being used in clinical practice, despite the limited data available [91]. Total response rates of 0–80 % have been observed with recombinant IFNα2b. A combination of treatments is feasible (acitretin, bexarotene, PUVA) and is well tolerated, though evidence in support of the superiority of retinoid combinations over IFNα2b monotherapy is lacking [92, 93]. Thus, a combination of IFNα2b with retinoids is recommended for patients with inadequate monotherapy success, or when combination with PUVA is contraindicated or unavailable [82]. Low-dosed methotrexate (MTX; 5 to 25 mg/week) is recommended for stage IIB or higher. It may be used as monotherapy or combined with bexarotene or IFNα2b [82, 94]. Intravenous chemotherapy, as monochemotherapy with pegylated liposomal doxorubicine or gemcitabine, is recommended for patients in the tumor stage with visceral involvement, for treatment of refractory/recurrent disease, or for "debulking" (reduction of tumor burden, a priori). Monochemotherapy is a preferred option because of lower toxicity, since polychemotherapy (such as cyclophosphamide-hydroxydaunorubicine-vincristine-prednisone, CHOP) has an unfavorable side effect profile without any proven survival benefit [95, 96]. Studies show total response rates of 67–75 % for gemcitabine and 41–88 % for liposomal doxorubicine [97–100]. The combination of chlorambucil, an alkylating agent, and low-dosed systemic prednisone (Winkelmann treatment scheme) is utilized for SS. Due to myelosuppression and an increased risk of leukemia, however, this is only recommended for short-term counselling [82].

Antibody therapy

Mycosis fungoides and Sézary syndrome are increasingly treated with antibody-based therapies, such as brentuximab vedotin or mogamulizumab.

Brentuximab vedotin (BV) is an antibody/cytostatic conjugate. In 2017, it was approved in Europe for treating recurrent or refractory CD30-positive CTCL. It consists of a monoclonal anti-CD30 IgG1 antibody and the antimitotic agent monomethylauristatin E. After incorporation into the tumor cell, it leads to cell cycle arrest and apoptosis. The primary endpoint of the licensing study for BV was the objective overall response rate for at least four months (ORR4) and was achieved by 56.3 % of patients. Progression free survival (PFS) was 63.9 % after twelve months and 28.8 % after 24 months. Total response rates of 55–70 % for CD30-positive CTCL (MF, SS, $CD30^+$ lymphoproliferative diseases) have been reported in the literature, with lower success rates when CD30 expression < 5 % [101–104].

Alemtuzumab, a monoclonal anti-CD52 antibody, is currently approved in Europe for treating multiple sclerosis. It was, however, initially designed for treating hematological disease. This antibody can be obtained free of charge for individual patients with erythroderma (T4) or involvement of the blood (B ≥ 1) via a special access program (www.clinigengroup.com) [82]. The standard dose is associated with a high rate of opportunistic infections, so low-dose treatment regimens have been established (such as 3–15 mg s.c. every other day). Response rates are comparable to the high-dose regimen, and the side effect profile is more acceptable [105].

Mogamulizumab, another monoclonal antibody, targets the CC chemokine receptor 4 (CCR4), which is expressed by tumor cells in CTCL. It works via antibody-dependent cell-mediated cytotoxicity (ADCC), defined as the destruction

of antibody-laden tumor cells by endogenous immune effector cells. This therapeutic antibody was approved in Europe in 2018 for treating patients with recurrent or refractory MF/SS after at least one previous systemic therapy. The pivotal study showed a significantly improved progression-free survival (PFS) for mogamulizumab as compared with the controls who received vorinostat (a histone-deacetylase inhibitor, not approved in the EU). Subgroup analysis showed better total response rates in SS patients with blood involvement than in MF patients [106].

Extracorporeal Photopheresis

Extracorporeal photopheresis is the first therapy specifically developed and approved for treating cutaneous T-cell lymphomas.

ECP, a leukapheresis-based immunomodulatory treatment, has been approved in Europe since 1987. Total response rates of about 60 % have been reported for erythrodermic MF/SS [107]. Historically speaking, ECP was the first therapy specifically developed and approved for treating CTCL. Leukocytes are enriched with 8-methoxypsoralen during extracorporeal circulation, and directly irradiated with UVA (365 nm). About 10–15 % of all nucleated cells are thus irradiated, usually on two consecutive days with two to four-week intervals [108, 109]. Re-infusion of the treated cell fraction is associated with systemic response after six to nine months; however, the mechanism of action is still unclear [110]. Recent data suggest that in Sézary syndrome, increased ADCC is associated with the response to ECP [111]. Combination of ECP with IFNα2b, retinoids, or phototherapy is common due to the excellent safety profile [82].

Allogeneic stem cell transplant

Allogeneic stem cell transplants are currently the only potentially curative therapeutic option for advanced mycosis fungoides and Sézary syndrome.

AlloSCT is currently the only potentially curative therapeutic option for advanced MF/SS [82].

Published data indicate an overall survival of 44 % and a PFS of 30 % seven years after alloSCT, which is encouraging [112–114]. In the absence of data regarding a standardized conditioning regimen (myeloablative vs. reduced intensity), there is currently no consensus on suitable patient characteristics for alloSCT. Nevertheless, this option should be considered in a timely/early manner for young patients, in cases with a high risk of disease progression, and/or in cases with a poor prognosis. For both indication and patient information, the search for a suitable donor as well as the occasionally high procedure-associated mortality must be taken into consideration [82].

Maintenance treatment

Apart from recent data on PUVA maintenance treatment [115] there is currently no clear evidence that maintenance treatment may offer a benefit. However, it should be considered especially for stage ≥ IIB patients with a high risk of recurrence and/or disease progression. Suitable options for maintenance treatment include topical corticosteroids, phototherapy, retinoids, IFNα2b, low-dosed MTX, and ECP. The choice of an appropriate maintenance treatment depends on efficacy, alleviation of symptoms, availability, handling, safety profile, and the lowest possible impairment of HRQoL [82].

In conclusion, one paradigm has remained constant in the treatment of CTCL for three decades: early, aggressive treatment, such as chemotherapy, does not improve prognosis compared to a sequential, stage-adapted treatment [116, 117]. However, the recent introduction of brentuximab vedotin as well as mogamulizumab has

fundamentally and positively impacted the therapeutic options for CTCL. Clinical studies are currently investigating further therapeutic antibodies for MF/SS, including promising candidates targeting KIR3DL2, CD47, or CD70, a bi-specific antibody targeting CD30 and CD16A, as well as a new IL-2 fusion toxin [118]. New discoveries on molecular characteristics, signal transduction, and tumor microenvironments in CTCL will most likely identify additional therapeutic targets in the future [102, 103].

Conclusion

CTCL are rare diseases. Adequate treatment requires a correct diagnosis, which in turn requires sufficient expertise regarding clinical presentation and dermatohistopathology. MF and its variants are the most common forms of CTCL. The prognosis for early-stage MF, the most common form, is usually good. SS *per se* is an advanced disease stage with a poor prognosis. It has been defined as an independent leukemic entity and is very rare. MF and SS are differentiated by clinical presentation (patch, plaque, tumor, erythroderma) and involvement of the peripheral blood. Apart from differing prognosis, the therapeutic approach also varies between MF and SS. Stage-appropriate, sequential treatment is generally recommended. SDT such as topical corticosteroids, topical chemotherapy, phototherapy, and radiotherapy are typically used in early-stage disease. Retinoids, IFNα2b, ECP, chemotherapy, and antibodies are administered for advanced or refractory disease. Ideally, these patients should be managed at specialized centers and, if required, on an interdisciplinary basis. This also facilitates or enables access to clinical studies. To date, alloSCT remains the only curative therapeutic option for MF/SS. Of note, alloSCT is associated with a high treatment-induced mortality and is currently only performed in a small number of patients. Thus, therapeutic palliation with the best possible HRQoL are the ultimate treatment goals for the majority of CTCL patients.

Disclosures

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CME Questions/Lernerfolgskontrolle

1. Welche Aussage für primär kutane Lymphome ist falsch?

a) Primär kutane T-Zell Lymphome (CTCL) machen 83 % aller kutanen Lymphome aus mit höherer Frequenz in Asien und Südamerika verglichen mit Europa.
b) Sie sind als seltene Erkrankungen (*orphan diseases*) klassifiziert und bilden nach den gastrointestinalen Magen-MALT-Lymphomen die zweithäufigste Gruppe der extranodalen Non-Hodgkin Lymphome.
c) Epigenetische Modifikation und dysfunktionale Regulation von Zytokinen und anderen Signalmolekülen werden diskutiert, bei der malignen Transformation von CTCL beteiligt zu sein.
d) Die aktuelle Klassifikation für kutane Lymphome, die WHO-EORTC Klassifikation 2018, ist eine Aktualisierung des Goldstandards aus dem Jahr 2005.
e) Bei CTCL weisen die neoplastische T-Zellen nicht nur die gleiche Morphologie (cerebriformer Nukleus), sondern auch einen gemeinsamen „T-Zell- Phänotyp“ auf.

2. Welche Aussage für die Mycosis fungoides (MF) ist richtig?

a) Klinisch ist für die MF ein stadienhafter Verlauf von *Patches* über Plaques bis hin zu Tumoren dokumentiert, eine Erythrodermie kommt niemals vor.
b) Patienten, die sich im *Patch*-Stadium der Erkrankung befinden, wechseln in der Regel nach wenigen Monaten ins Plaque-Stadium und anschließend ins Tumor-Stadium.
c) Die Prognose der MF ist im Frühstadium der Erkrankung vorteilhaft.
d) Die pagetoide Retikulose ist keine Variante der MF.
e) Die histologischen Merkmale der MF sind stets in jeder Hautbiopsie eindeutig.

3. Welche Aussage zum Sézary-Syndrom (SS) ist falsch?

a) Das SS ist klassischerweise durch eine Erythrodermie, Lymphadenopathie und Sézary-Zellen in Blut gekennzeichnet.
b) Als Symptome des SS wurden auch palmoplantare Hyperkeratosen, Onychodystrophie, Alopezie, Facies leonina und Ektropium angeführt.
c) Beim SS handelt es sich um ein leukämisches kutanes T-Zell-Lymphom mit ungünstiger Prognose.
d) Central-Memory-T-Zellen wurden als Ursprungszellen des SS identifiziert, diese zirkulieren zwischen Haut, Lymphknoten und Blut und spielen eine wichtige Rolle für die Kommunikation dieser Kompartimente.
e) Das SS ist die leukämische Variante des MF und somit als MF-Subtyp klassifiziert.

4. Welche der folgenden Aussagen zu Diagnostik und Staging bei Mycosis fungoides (MF) und Sézary-Syndrom (SS) gemäß der S2-k-Leitlinie ist falsch?

a) Diagnostik und Staging von MF und SS basieren auf Anamnese, klinischer, histologischer und hämatologischer Untersuchung sowie bildgebenden Verfahren.
b) Zur Diagnosestellung sind Knochenmarksbiopsien stets indiziert.
c) Wichtige Methoden bei Laboruntersuchungen sind unter anderem, Durchflusszytometrie und Klonalitätsanalyse im Blut.
d) Bei Staging-Untersuchungen kommen als bildgebende Verfahren unter anderem chest X-ray, Abdomen- und Lymphknotensonographie sowie Ganzkörper-CT zum Einsatz.
e) Zu den klinischen Untersuchungen gehören unter anderem detaillierte Erfassung des Hautbefunds und den Lymphknotenstatus.

5. Welche Differenzialdiagnosen müssen bei Sézary-Syndrom (SS) nicht berücksichtigt werden?

a) erythrodermatische MF
b) Psoriasis
c) atopische Dermatitis
d) Pityriasis rubra pilaris
e) Small-Patch-Parapsoriasis

6. Welche Aussage zur Ausbreitungsdiagnostik (*Staging*) von Mycosis fungoides (MF) und Sézary-Syndrom (SS) gemäß ISCL/EORTC ist falsch?

a) Die Stadieneinteilungen der beiden Erkrankungen basieren auf der TNMB-Klassifikation.
b) Das SS wird aufgrund seiner zwingenden Blutbeteiligung (Sézary-Zellen > 1000/µl im peripheren Blut) immer mindestens dem Stadium IVA1 zugeordnet.
c) B2 ist definiert durch: eine absolute Sézary Zellzahl von > 1000/l oder eine erhöhte $CD4^+$-T-Zellpopulation, $CD4^+/CD8^+$-Verhältnis ≥ 10, $CD4^+/CD7^-$-Zellen ≥ 40 % oder $CD4^+/CD26^-$-Zellen ≥ 30 %.
d) Der Nachweis von Sézary-Zellen im peripheren Blut spielt eine nur untergeordnete Rolle.
e) Wird die Blutbeteiligung als B0 klassifiziert, sind weniger als 5 % atypische Lymphozyten beziehungsweise Sézary-Zellen im peripheren Blut nachweisbar.

7. Welche Aussage zur Prognose bei Patienten mit Mycosis fungoides (MF) beziehungsweise Sézary-Syndrom (SS) trifft zu?

a) Die mittlere krankheitsspezifische 5-Jahres-Überlebensrate bei MF im Stadium IA beträgt 89 %.
b) Männliches Geschlecht ist ein günstiger Prognosefaktor.
c) Für Patienten mit hypopigmentierter MF oder einer MF mit lymphomatoider Papulose wurde ein besseres Gesamtüberleben beziehungsweise

ein reduziertes Progressionsrisiko belegt.
d) Alter und Geschlecht beeinflussen die Prognose nicht.
e) Die mittlere krankheitsspezifische 5-Jahres-Überlebensrate bei MF im Stadium IIIB liegt noch bei über 50 %.

8. Welche *First-Line*-Therapien werden von der EORTC in ihrer aktuellen Leitlinie zur Behandlung des Sézary-Syndroms (SS) empfohlen?
a) ECP, Chlorambucil und Kortikosteroid, ECP/PUVA plus Retinoide/IFNα, niedrig dosiertes MTX
b) ECP, Chlorambucil und Kortikosteroid, ECP/PUVA plus Retinoide/IFNα, Alemtuzumab
c) ECP, Chlorambucil und Kortikosteroid, Chemotherapie, Alemtuzumab
d) niedrig dosiertes MTX, Chemotherapie
e) ECP, Chlorambucil und Kortikosteroid, Alemtuzumab

9. Welche Aussage zur Therapie der Mycosis fungoides (MF) gemäß EORTC trifft zu?
a) Haut-gerichtete Therapieschemata erfolgen nur im frühen Stadium der Erkrankung.
b) Systemische Therapien kommen nur im fortgeschrittenen Stadium der Erkrankung zum Einsatz.
c) Jede MF wird ausnahmslos nach der Diagnosesicherung therapiert.
d) Die Therapie der MF erfolgt stadiengerecht mit Berücksichtigung bereits verabreichter Vortherapien, der Präferenz und der gesundheitsbezogenen Lebensqualität der Patienten.
e) Methotrexat in niedriger Dosierung wird als First-Line-Therapie bei einer MF im Stadium IA bis IIA empfohlen.

10. Welche Aussage zum Management von Patienten mit Mycosis fungoides (MF) beziehungsweise Sézary-Syndrom (SS) ist falsch?
a) Die korrekte Diagnosestellung von MF/SS setzt eine ausreichende Expertise hinsichtlich Klinik und Dermatohistopathologie voraus.
b) In frühen Stadien der MF kommen vorwiegend SDT wie topische Kortikosteroide, topische Chemotherapie, Photo- und Radiotherapie zum Einsatz. Bei fortgeschrittener oder refraktärer Krankheit werden Retinoide, IFNα2b, ECP, Chemotherapie und Antikörper angewendet.
c) Aktuell ist bei MF/SS die allogene Stammzelltransplantation die einzig kurative Therapieoption und wird daher bei der Mehrheit der Patienten durchgeführt.
d) Der Therapieansatz für MF/SS ist mehrheitlich palliativ.
e) Die Betreuung von MF/SS-Patienten in spezialisierten Zentren ermöglicht den Zugang zu klinischen Studien.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 30. November 2021. Die richtige Lösung zum Thema „Die (neue) Berufskrankheit Nr. 5101: „Schwere oder wiederholt rückfällige Hauterkrankungen“ in Heft 5 (Mai 2021) ist: (1a, 2d, 3d, 4c, 5b, 6e, 7c, 8e, 9a, 10b).

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.

