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None.

Importance of diagnostics and risk of secondary malignancies in primary cutaneous lymphomas

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Summary

Background and Objectives: Primary cutaneous lymphomas (PCL) often strongly differ in clinical behavior and prognosis from systemic lymphomas of the same histopathologic type. The aim of the study was to investigate the distribution of PCL subtypes, the average time from disease manifestation to diagnosis, the importance of diagnostic procedures, the occurrence of secondary malignancies and the different treatment modalities.

Patients and Methods: Retrospective analysis of 152 patients with PCL examined at the Department of Dermatology of the University Hospital Tübingen from 2010–2012.

Results: 105 patients with CTCL (69.1 %) and 47 patients with CBCL (30.9 %) were included. The average time from disease manifestation to diagnosis was four years. The most common diagnosed lymphoma was mycosis fungoides (MF) (47.4 %). First-line therapies here include phototherapy only (psoralen-UV-A [PUVA], n = 48; UVB 311 nm, n = 7) or combination therapies primarily phototherapy with systemic retinoids (n = 18). Most frequent second-line therapy was interferon (INF)-α plus PUVA (n = 15). The outcome was favorable (45.2 % remission, 28.6 % stable disease, 22.6 % progressive disease). Malignant comorbidities were observed more frequently compared to a healthy control group.

Conclusions: The diagnosis of lymphoma often takes several years. The value of staging procedures is still low and the treatment modalities for MF in earlier stages are mainly based on phototherapy.

Introduction

Primary cutaneous lymphomas (PCL) are a heterogeneous group of extra nodal non-Hodgkin-lymphomas (NHL). According to the WHO definition PCL is present in the skin without evidence of extracutaneous manifestations at the time of diagnosis [1]. This is to be differentiated from secondary cutaneous lymphoma in which the skin is one manifestation site of systemic extracutaneous lymphoma including leukemia. With an annual incidence of about 1 : 100.000 PCL are relatively rare, but they are the second most common type of extra nodal NHL after primary gastrointestinal lymphomas [2]. Cutaneous T-cell lymphoma (CTCL) with its several entities represents the largest group with almost three quarters of all PCL, while cutaneous B-cell lymphomas (CBCL) are less common [3–7].

In 1997, the lymphoma study group of the *European Organisation for Research and Treatment of Cancer* (EORTC) proposed a classification for cutaneous lymphomas. This EORTC-Classification applies a combination of clinical, histological and immunohistochemical criteria to define the different disease entities [8]. In 2005, it was replaced by the WHO-EORTC consensus classification [7] which was updated in 2007 [9, 10] and 2017/2018 [11, 12] and incorporated into the most recent WHO classification [1]. In 2018, recommendations for classification of blood parameter changes and blood response criteria in mycosis fungoides (MF) and Sézary syndrome using flow cytometry were added [13].

In view of the new guidelines and classification published in 2019 [1], the aim of this retrospective study was to investigate the distribution of PCL subtypes and to evaluate diagnostic latency, the impact of diagnostic procedures, the incidence of malignant comorbidities and the different treatment modalities within the course.

Patients, materials and methods

Subjects and data collection

Patients with PCL, who were treated in the specialized cutaneous lymphoma consultation at the Department of Dermatology, University of Tübingen, between 2010 and 2012, were included. The patients were identified, selected and pseudonymized over three years using the medical report archive. Patients with insufficient data and less than two visits were excluded.

Data collected included patient age, sex, date of initial manifestation as reported by the patient, date of definite diagnosis confirmed by histology, comorbidities, follow-up time; type, site and extent of lesion, lymph node status, B-symptoms, results of staging procedures including radiology reports, bone marrow examination, lymph node histology, Sézary-cells, CD4/CD8-ratio and *Borrelia* serology, therapies and the last disease stage. Diagnoses were assessed according to the WHO/EORTC classification.

Follow-up

Follow-up was done through regular specialized PCL outpatient consultations. Special cases were discussed in an interdisciplinary lymphoma board. The study was approved by the ethics commission of Tübingen University.

Statistical analysis

The analysis was performed by descriptive statistical methods (absolute/relative frequency distribution, mean value) with SPSS® (software version 15.0) program and Prism Graph Pad.

Results

Demographics

A total of 152 patients with PCL (CTCL n = 105; CBCL n = 47) were included. The gender ratio was m : w = 1.45 : 1 (90 male, 62 female). Patients were observed on average for 5.8 years (range: 1–26 years). The most common PCL subtype was MF with a frequency of 47.4 % (72 patients) and a male predominance (50 male, 22 female, m : f = 2.2 : 1). Further frequent subtypes were lymphomatoid papulosis (LyP; 8.6 %) and C-ALCL (5.3 %) for the CTCLs. Regarding the CBCLs, follicle center lymphoma (13.8 %) marginal zone B-cell lymphoma (9.2 %) and diffuse large B-cell lymphoma, leg-type (4.6 %) were common. Median age at time of diagnosis for PCL was 56.9 years (range: 2–89 years). Table 1 lists frequency, age at diagnosis and observation period of each entity and classifies the patient cohort according to the revised WHO/EORTC classification [1].

MF was mainly diagnosed in earlier stages (58 cases with a documented stage at the time of diagnosis; stage I: 63.8 %, stage II: 17.3 %, stage III: 10.3 %, stage IV: 10.3 %). Table 2 shows malignant comorbidities in patients with MF and CD30⁺ lymphoma (LyP, primary cutaneous anaplastic large cell lymphoma [C-ALCL]).

Diagnostics

The time span from clinical manifestation to the definitive diagnosis for PCL (n = 117) showed a wide range and was quite long with 4 ± 7 years (mean ± SD, range: 1 month–45.7 years). For MF (n = 58) this timespan was even longer with 6.1 ± 8.6 years (mean ± SD, range: 1 month–45.7 years). CD30⁺ entities were diagnosed faster (LyP: mean 2.4 ± 4.2 years, range: 1 month–12 years; C-ALCL: mean 1.3 ± 1.9 years, range: 1 month–4.9 years) (Figure 1). The latency was 2.9 ± 5.7 years (mean ± SD, range 1 month–24.8 years) for follicle center lymphoma, 2.3 ± 2.8 years (mean ± SD, range 1 month–8.6 years) for marginal zone BCL and 0.6 ± 0.4 years (mean ± SD, range 8 month–1.4 years) for diffuse large BCL.

Subtype and stage-dependent staging investigations were performed according to the guidelines [3]. For MF patients, there was no lymphoma-specific result in all 57 chest x-rays and in all 58 abdominal sonographies performed (Figure 2). The Sézary cell count was elevated in six cases (6/57; 11 %). Three of those patients were subsequently diagnosed with Sézary syndrome. The CD4/CD8-ratio showed elevated CD4 cells in ten cases (10/36; 28 %). Two of these patients were subsequently diagnosed with Sézary syndrome. In patients with LyP and C-ALCL we performed 18 abdominal sonographies, 17 chest X-rays, 12 blood films and four FACS analyses for the CD4/CD8-ratio (Figure 2). All tests, except a single chest X-ray, were unremarkable. Here, retrohilar condensations without lymphoma specific changes were found in the subsequently performed CT scan. Further diagnostic results are listed in a supplementary Table S1 (online Supporting Information).

Therapy and Outcome

Fifty-five of 72 patients with MF received phototherapy (PUVA bath or systemic n = 48; UVB 311 nm phototherapy

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Table 1 Demographic data divided in subtypes corresponding to WHO/EORTC classification, age of the patient and duration of clinical observation.

Cutaneous lymphomas with primary cutaneous manifestations (WHO-EORTC classification 2018 [10])	Patients, n =	Frequency, %	Age at diagnosis, [years] Mean; Range	Observation period, [years] Mean; Range
Cutaneous T-cell and NK-cell lymphomas	*105*	*69.1*	*55.3; 2–87*	
Mycosis fungoides (MF)	72	47.4	57.1; 9–89	6.3; 1–26
MF variants	1	0.7	81	2
– folliculotropic MF	0			
– pagetoid reticulosis	1	0.7	81	2
– granulomatous slack skin	0			
Sézary syndrome	4	2.6	57.8; 42–70	5.0; 2–8
Adult T-cell leukemia/lymphoma	0			
Primary cutaneous $CD30^+$ lymphoproliferative disorders	21	13.8	49.1; 2–87	5.7; 1–16
– anaplastic large cell lymphoma	8	5,3	59.9; 29–78	4.5; 1–11
– lymphomatoid papulosis	13	8,6	42.5; 2–87	6.5; 1–16
Subcutaneous panniculitis-like TCL	2	1,3	68.0; 62–74	7.0; 5–9
Extra nodal NK/T-cell lymphoma, nasal type	0			
Chronic active EBV infection	0			
Primary cutaneous peripheral TCL, rare subtypes*	6	3,9	55.0; 38–77	5.0; 1–9
– aggressive epidermotropic $CD8^+$ TCL (provisional)	3	2	51.3; 38–77	5.0; 4–6
– primary cutaneous γ/δ TCL	0			
– primary cutaneous $CD4^+$ small/medium pleomorphic T- cell lymphoproliferative disorder (provisional)	3	2	58.7; 53–66	5.0; 1–9
– Primary cutaneous acral CD8+ T- cell lymphoma (provisional)	0			
Primary cutaneous peripheral TCL, NOS	0			
Cutaneous B-cell lymphomas	*47*	*30.9*	*59.8; 13–86*	
Marginal zone BCL	14	9,2	59,4; 13–78	3.3; 1–11
Follicle center lymphoma	21	13.8	52.4; 29–77	8.0; 1–25
Diffuse large BCL, leg type	7	4.6	77.9; 65–86	2.9; 1–5
Diffuse large BCL, other	5	3,3	66.6; 44–77	4.0; 2–9
– intravascular large BCL	0			
EBV1 mucocutaneous ulcer (provisional)	0			
Total	*152*	*100*	*56.9; 2–89*	*5.8; 1–26*

Table 2 Malignant comorbidities in patients with mycosis fungoides and CD30⁺ lymphoma.

Comorbidities	Mycosis fungoides	CD30⁺ lymphomas
Skin tumors	9	2
Hematological malignancies	2	0
Solid tumors	5	6

n = 7) as first-line therapy. In 18 cases (15 with stage IIb or higher), PUVA-therapy was used in combination with systemic retinoids. Other first-line therapies were shown in Figure 3. The most common second-line therapy was to escalate the ongoing PUVA with INF-α (n = 15). Following topical steroids or UVB311, PUVA was started in ten patients. Upon progression of the disease, radiotherapy (n = 7) and low-dose methotrexate (n = 4) were indicated. Third-line chemotherapy was polychemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or fludarabine plus cyclophosphamide (n = 5) or mono-chemotherapy with Bortezomib (n = 1) and gemcitabine (n = 1). One patient underwent allogeneic stem cell transplantation after four cycles of CHOP (Figure 4). Low-grade CBCL could be treated in 57.1 % (n = 20) by excision or local radiotherapy (40–50 Gy). 8.6 % (n = 3) benefited from a combination of both therapies, from a combination of one or both therapies with rituximab or interferon intralesional (22.9 %, n = 8) or a monotherapy with intralesional injections of rituximab (2.9 %, n = 1). In one patient with follicle center lymphoma only clinical controls were performed (2.9 %, n = 1). One patient suffered from multiple malignancies and received palliative therapy (2.9 %, n = 1). In six patients with CBCL polychemotherapy (CHOP, Rituximab [R]-CHOP) was performed. Diffuse large BCL required systemic chemotherapy in 42.7 % (n = 5).

The outcome was favorable in MF and CD30⁺ lymphomas. The last documented status of 84 patients with MF and CD30⁺ lymphomas was remission in 45.2 % (n = 38), stable disease in 28.6 % (n = 24), progression in 22.6 % (n = 19) and only 3.6 % (n = 3) of patients died of the PCL. The last status could not be determined reliably in nine patients (status uncertain, death due to other cause). In detail, patients with MF achieved remission in 33.3 % (n = 21) or stable disease in 33.3 % (n = 21). In 28.6 % (n = 18) there was progress, 4.8 % (n = 3) died due to MF or consequences related to it. Patients with LyP had remission in 76.9 % (n = 10) and stable disease

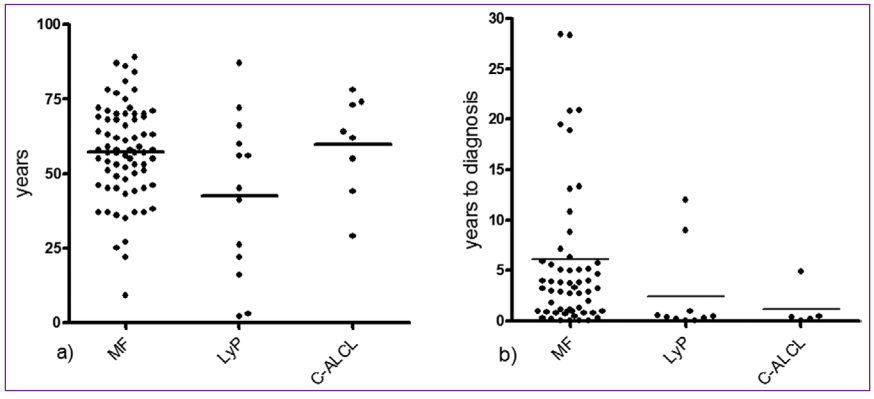

Figure 1 Age (a) and latency from first noted manifestation to definite diagnosis (b) in mycosis fungoides (MF), lymphomatoid papulosis (LyP) and primary cutaneous CD30-positive large cell lymphoma (c-ALCL).

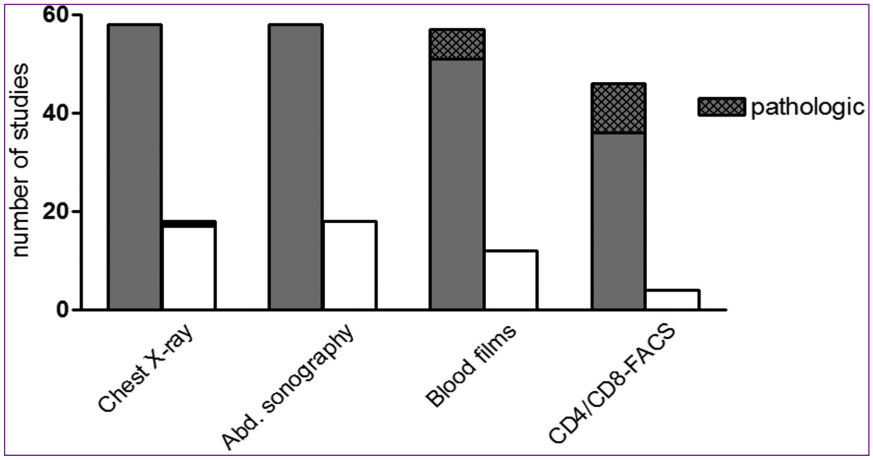

Figure 2 Diagnostic impact of staging procedures in mycosis fungoides (grey bars) or CD30-positive lymphoproliferative diseases (white bars). Pathological results are marked a with black pattern.

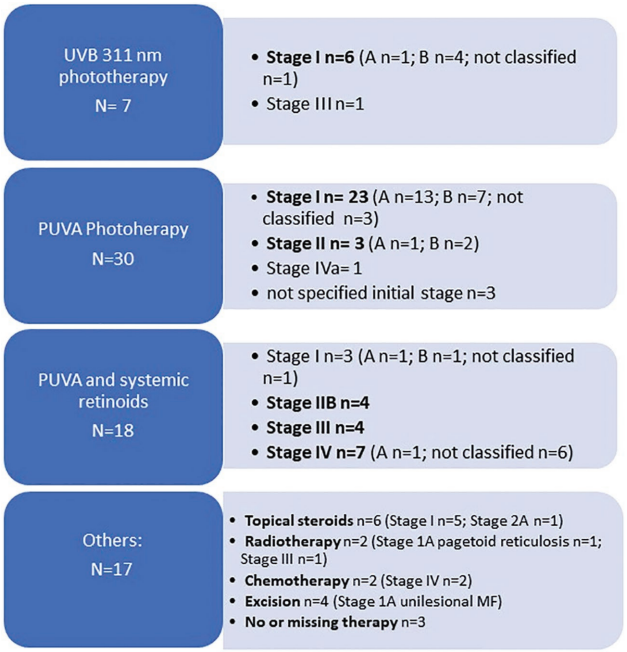

Figure 3 Stage-adapted first-line therapy of patients with mycosis fungoides.

in 23.1 % (n = 3). In C-ALCL, remission occurred in 87.5 % (n = 7) and one patient (12.5 %) showed disease progression.

Discussion

Against the background of the new guidelines and classification published in 2019 [1], the main purpose of this study was to characterize a German single-center cohort with PCL. A comparison of our cohort with published cohorts showed that the demographics of our patient group matches the data from the study of Bradford et al. [14], the data published by the Dutch and Austrian Cutaneous Lymphoma Group [7] and a recent U.K. National Cancer Information audit of newly diagnosed cases of CTCL [15] throughout the lymphoma subtypes. This indicates that our collective is a representative patient group (Table 3).

Primary cutaneous lymphomas are generally a disease of late adulthood [14, 15]. Confirming this, we observed a peak incidence of PCL in the 6th decade of life. LyP was an exception, with a peak around the age of 45 years. However, the range of manifestation age is enormous: PCL can also affect young persons and even children [7, 16, 17]. Our youngest patients were two-year-old and three-year-old children with LyP, a nine-year-old boy with MF and a 13-year-old boy with marginal zone BCL. This shows the importance of keeping the differential diagnosis of a PCL for children as well as for adults in mind, and serves to encourage biopsies of suspicious lesions in any age group. For LyP this is particularly important in children as LyP type C is histologically identical to CD30+ diffuse large adult T-cell leukemia/lymphoma (ATL), which in systemic cases would be treated aggressively. Lymphomatoid papulosis has chronic recurrence, but nodules are self-healing and prognosis is favorable; therefore no aggressive therapy is indicated [4, 16].

The long timespan between onset of symptoms and the definite diagnosis corresponds with recent data of a multinational web-based data collection system, in which 85.6 % of 430 patients with MF showed a diagnostic delay [18]. The mean delay was 36 months, similar to the 48 months observed in our cohort. This demonstrates the challenges in the diagnosis of PCLs. Especially MF is known as a great imitator of inflammatory skin diseases like eczema, psoriasis or chronic actinic dermatitis [19]. This includes clinical symptoms and histopathology in early stages of MF, which might be unspecific and possibly altered by treatment, such as topical steroids [20]. Often multiple biopsies are needed to ensure diagnosis. Furthermore, the course of MF is indolent with slow progression over the years. Due to similar treatment regimes in eczema mimicking MF and MF itself,

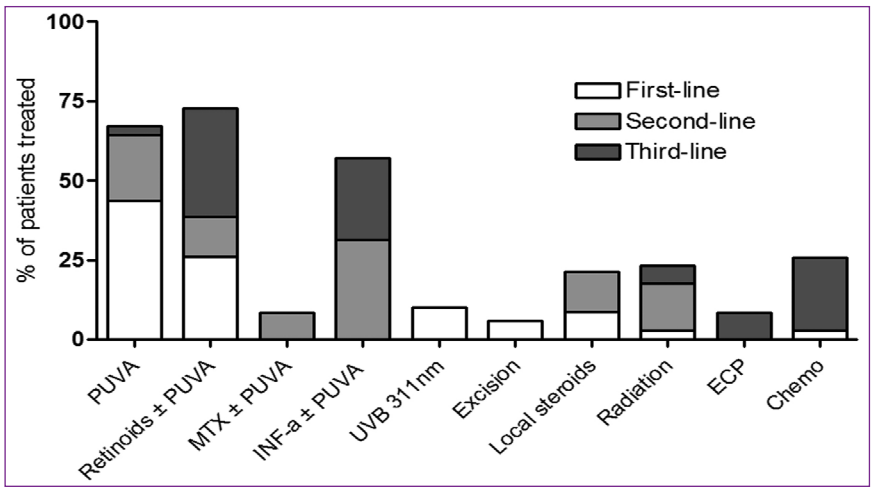

Figure 4 First-, second-, and third-line therapies in mycosis fungoides. Each bar represents the percentage of the treatment option as first-, second-, or third-line treatment.

Table 3 Distribution of primary cutaneous lymphomas (PCL) in lymphoma subtypes in our cohort compared to the Dutch lymphoma group [2].

Lymphoma type	Current collective	Willemze et al. [2]
Cutaneous T-cell lymphomas		
Mycosis fungoides (MF)	47.4 %	44.0 %
Sézary syndrome	2.6 %	3.0 %
Anaplastic large cell lymphoma	5.3 %	8.0 %
Lymphomatoid papulosis (LyP)	8.6 %	12.0 %
Cutaneous B-cell lymphomas		
Marginal zone BCL	9.2 %	7.0 %
Follicle center lymphoma	13.8 %	11.0 %
Diffuse large BCL	3.3 %	>5.0 %

treatment efficacy can mask the original presentation further delaying the correct diagnosis. Similarly, for other PCL it can take years before the definite diagnosis is set. This is either due to an unawareness of rare entities, such as LyP in children, or because histological and clinical findings are misleading.

Staging procedures are indicated regarding the lymphoma type and disease stage [3]. Almost all radiological procedures in our study presented normal results, questioning the need for chest x-ray and sonography in early stage MF or CD30⁺ lymphoproliferative disorders. In contrast to CBCLs, CTCLs are generally very rarely of secondary cutaneous origin. However, the detection of extracutaneous involvement is of high prognostic and therapeutic relevance. These radiological staging procedures are not harmful to patients and they are cheap, easy to perform and are probably still worthy of consideration. They deliver a baseline result that can be compared against when rapid progression occurs. Some PCLs, especially LyP, can be associated with other types of malignant lymphomas, such as MF, CD30⁺ large TCL with systemic involvement or other systemic NHL [16]. In conclusion, although our data question the diagnostic validity of radiological procedures it still seems reasonable to perform staging at the point of diagnosis of early stage CTCL including chest x-ray and abdominal sonography. In our experience, they should only be repeated later if progression is suspected. For CBCL these investigations are essential for excluding extracutaneous involvement as cutaneous B cell infiltrates can often be signs of systemic disease [21]. However, due to increased sensitivity in rapidly progressing cases or in high-grade lymphomas a CT or even PET-CT is indicated [22].

In this study, therapy was implemented in a stage-adapted manner as recommended in the guidelines [4]. An exception is the excisions performed in the cases of unilesional MF. The literature on this special form is inconsistent and different therapeutic approaches are described. Several case series support excision as a possible therapeutic option even if it is not explicitly recommended in the guidelines [23]. For early stage MF (stage Ia to IIb) stable disease or remission could be achieved using skin directed therapies, such as phototherapy or topical steroids. In rare cases, a combination of PUVA and systemic retinoids or INF-α was additionally recommended as the first-line option. In accordance with our study, the Italian lymphoma registry showed ten-year survival rates of 93 % for stage Ia, 86 % for stage Ib and 72 % for stage IIa MF [24]. Especially for PUVA therapy as monotherapy or in combination with INF-α or systemic retinoids, high remission rates are seen that can last many years [25, 26]. Therapy was changed in case of disease progression, but also upon occurrence of side effects or poor compliance. Since PUVA therapy has to be administered several times a week for several months, it was discontinued in some cases because it was too time consuming to integrate into the patient's daily life. Therefore, therapies had to be changed even if they were effective. Recently, however, a low-dose, low frequency maintenance PUVA treatment was shown to be highly effective [27], confirming the beneficial effect of PUVA in our collective. In more advanced MF stages (stage IIb and higher) the treatment needs to be escalated, as they are associated with a poorer prognosis. For MF stage IIb and stage III ten-year survival rates of about 50 % are common, while prognosis is very poor for stage IV with five-year survival rates of about 25 % [24]. Even in these MF stages PUVA therapy is effective and serves as a cornerstone of therapy, often combined with systemic retinoids and/or INF-α [4, 26]. In our collective we could induce remissions in many cases but relapses were also frequent. Aggressive chemotherapies like gemcitabine, doxorubicin or CHOP were only used as *ultima ratio* in the treatment of advanced MF, because responses are often followed by rapid disease progression and poor course [28]. For these cases new concepts for targeted therapy strategies have been developed [29]. Brentuximab vedotin directed against the surface molecule CD30, which is expressed in most advanced MF, Sézary syndrome and CD30⁺ lymphoproliferative diseases, was approved in 2018 for second-line therapy [30, 31]. Since 2019, the anti-CCR4 antibody mogamulizumab has been approved as another second-line option [32]. In addition allogeneic hematopoietic stem cell transplantation, reported to have curative potential [33] but also a high rate of treatment associated mortality, should be considered in highly selected patients. In our collective, a single patient underwent allogeneic HCT after four cycles of CHOP. This patient died one year later. Low-grade CBCL (primary cutaneous marginal zone BCL, follicle center lymphoma) were treated

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with excision, radiotherapy or intralesional injections with interferon-α or rituximab [4, 34]. In our collective, 91.4 % of all low-grade CBCL could be treated with one of these therapies. As described in the literature [4, 15], diffuse large BCL (leg-type or other) are more aggressive lymphomas and, as in our study, often required systemic chemotherapy. In addition to established chemotherapies (R-CHOP), CD20 antibodies such as obinutuzumab or ofatumumab [35] or immunoregulatory drugs such as lenalidomide [36] represent new treatment alternatives.

Patients with CTCLs have an increased risk of developing secondary malignancies, particularly secondary lymphomas [37]. In some studies an increased risk of secondary cutaneous malignancies, urogenital cancer, leukemia, biliary cancer, colon and lung cancer were demonstrated. However, there are inconsistencies in the type of associated malignancies and the magnitude of the reported risk increase [38–41]. In our study, 72 patients with MF developed 16 malignant comorbidities (9 malignant skin tumors, 5 solid tumors, 2 hematological malignancies) in a median observation period of 6.3 years. This is about twice as much as expected for a healthy population adjusted to the median age of our collective of 57.1 years. In terms of the development of secondary malignant skin tumors (5 basal cell carcinomas, 3 squamous cell carcinomas,1 lentigo maligna melanoma) therapy-induced effects, especially increased exposure to UV-radiation, can be blamed. All patients that developed a potentially UV-induced malignancy underwent PUVA or Re-PUVA. It is known that PUVA-therapy can induce squamous cell carcinoma and also more rarely basal cell carcinomas, but this effect is described mainly for patients that underwent at least 150 PUVA treatments [42]. In our study, most patients had only a few months of PUVA-therapy, which makes it very unlikely that PUVA is the only direct cause. However, exposure to natural UV radiation can also often be higher in MF patients than in healthy individuals, as many MF patients like to sunbath to improve their skin. Overall, we suspect that cumulative exposure to UV radiation is an important factor for the development of secondary skin malignancies in MF patients. Incidence rates may be biased due to more extensive and frequent screening examination in CTCL patients than in healthy individuals. This also applies to the diagnosis of solid tumors and hematological malignancies in MF patients. Especially in the case of slowly growing or indolent malignant tumors (e.g. prostate cancer), extended staging procedures can lead to a higher incidence rate of otherwise incipient carcinomas [43]. Another reason for the higher incidence rate can be a dysfunctional immune surveillance favoring cancer development [39, 40]. However, in our study the case number was too low to evaluate the rate of solid tumors in CTCL patients. Nevertheless, since the follow-up recommendations of the current guideline are based on insufficient data, were only established for patients with complete remission, and provide imprecise follow-up intervals for higher stages of MF and Sézary syndrome [4], our data may help to substantiate the guideline not only for the detection of secondary lymphomas but also for the detection of other common secondary malignancies at an early stage in CTCL patients. Patients should be informed and motivated to follow recommended interventions and timelines of established cancer screening programs and to have dermatological full-body inspections performed according to close follow-up intervals of high-risk skin cancer patients.

Limitations

Limitations include the small patient number in the various subgroups and the retrospective monocentric design. At the time of data collection, no novel treatment methods were available. In the future, their application could change the outcome results, especially at higher lymphoma stages. Currently, the new therapies still play a subordinate role and are only used in studies or in advanced cases.

Conclusions

Primary cutaneous lymphoma often take several years to be diagnosed. This underlines the difficulties in accurate diagnosis, which includes misleading histological and clinical findings and a lack of a singular diagnostic test, especially for MF. Primary cutaneous lymphomas are generally a disease of late adulthood, but must also be kept in mind as a rare diagnosis in children. The value of the staging procedures used is limited. Treatment modalities in earlier MF stages are still dominated by phototherapy despite new therapy options. Due to an increased incidence of secondary tumors, appropriate monitoring for early detection of secondary cancers may be warranted.

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References

1 Willemze R, Cerroni L, Kempf W et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019; 133(16): 1703–14.

2 Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000; 92(15): 1240–51.

3 Dippel E, Assaf C, Becker JC et al. S2k Guidelines – Cutaneous Lymphomas Update 2016 – Part 1: Classification and Diagnosis (ICD10 C82 - C86). J Dtsch Dermatol Ges 2017; 15(12): 1266–73.

4 Dippel E, Assaf C, Becker JC et al. S2k Guidelines – Cutaneous Lymphomas Update 2016 – Part 2: Treatment and Follow-up (ICD10 C82 - C86). J Dtsch Dermatol Ges 2018; 16(1): 112–22.

5 Felcht M, Klemke CD, Nicolay JP et al. Primary cutaneous diffuse large B-cell lymphoma, NOS and leg type: Clinical, morphologic and prognostic differences. J Dtsch Dermatol Ges 2019; 17(3): 275–85.

6 Nicolay JP, Wobser M. Cutaneous B-cell lymphomas – pathogenesis, diagnostic workup, and therapy. J Dtsch Dermatol Ges 2016; 14(12): 1207–24.

7 Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105(10): 3768–85.

8 Willemze R, Kerl H, Sterry W et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 1997; 90(1): 354–71.

9 Olsen E, Vonderheid E, Pimpinelli N et al. Revisions to the staging and classification of 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(6): 1713–22.

10 Kim YH, Willemze R, Pimpinelli N et al. 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(2): 479–84.

11 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.

12 Willemze R, Hodak E, Zinzani PL et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29 (Suppl. 4): iv30–40.

13 Scarisbrick JJ, Hodak E, Bagot M et al. Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. Eur J Cancer 2018; 93: 47–56.

14 Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009; 113(21): 5064–73.

15 Gilson D, Whittaker SJ, Child FJ et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol 2019; 180(3): 496–526.

16 Bekkenk MW, Geelen FA, van Voorst Vader PC et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000; 95(12): 3653–61.

17 Kempf W, Kazakov DV, Belousova IE et al. Paediatric cutaneous lymphomas: a review and comparison with adult counterparts. J Eur Acad Dermatol Venereol 2015; 29(9): 1696–709.

18 Scarisbrick JJ, Quaglino P, Prince HM et al. The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. Br J Dermatol 2019; 181(2): 350–7.

19 Zackheim HS, McCalmont TH. Mycosis fungoides: the great imitator. J Am Acad Dermatol 2002; 47(6): 914–8.

20 Santucci M, Biggeri A, Feller AC et al. Efficacy of histologic criteria for diagnosing early mycosis fungoides: an EORTC cutaneous lymphoma study group investigation. European Organization for Research and Treatment of Cancer. Am J Surg Pathol 2000; 24(1): 40–50.

21 Eberle FC, Metzler G, Weisel KC et al. Cutaneous presentation of hematological malignancies. Eur J Dermatol 2013; 23(3): 372–7.

22 Kuo PH, McClennan BL, Carlson K et al. FDG-PET/CT in the evaluation of cutaneous T-cell lymphoma. Mol Imaging Biol 2008; 10(2): 74–81.

23 Ally MS, Pawade J, Tanaka M et al. Solitary mycosis fungoides: a distinct clinicopathologic entity with a good prognosis: a series of 15 cases and literature review. J Am Acad Dermatol 2012; 67(4): 736–44.

24 Quaglino P, Pimpinelli N, Berti E et al. Time course, clinical pathways, and long-term hazards risk trends of disease progression in patients with classic mycosis fungoides: a multicenter, retrospective follow-up study from the Italian Group of Cutaneous Lymphomas. Cancer 2012; 118(23): 5830–9.

25 Oguz O, Engin B, Aydemir EH. The influence of psoralen + ultraviolet A treatment on the duration of remission and prognosis in mycosis fungoides. J Eur Acad Dermatol Venereol 2003; 17(4): 483–5.

26 Chiarion-Sileni V, Bononi A, Fornasa CV et al. Phase II trial of interferon-alpha-2a plus psolaren with ultraviolet light A in patients with cutaneous T-cell lymphoma. Cancer 2002; 95(3): 569–75.

27 Vieyra-Garcia P, Fink-Puches R, Porkert S et al. Evaluation of low-dose, low-frequency oral psoralen-uv-a treatment with or without maintenance on early-stage mycosis fungoides: a randomized clinical trial. JAMA Dermatol 2019; 155(5): 538–47.

28 Alberti-Violetti S, Talpur R, Schlichte M et al. Advanced-stage mycosis fungoides and Sézary syndrome: survival and response to treatment. Clin Lymphoma Myeloma Leuk 2015; 15(6): e105–12.

29 Hristov AC, Tejasvi T, Wilcox RA. Mycosis fungoides and Sézary syndrome: 2019 update on diagnosis, risk-stratification, and management. Am J Hematol 2019; 94(9): 1027–41.

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30 Prince HM, Kim YH, Horwitz SM et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 2017; 390(10094): 555–66.
31 Shea L, Mehta-Shah N. Brentuximab Vedotin in the Treatment of peripheral t cell lymphoma and cutaneous T cell lymphoma. Curr Hematol Malig Rep 2020; 15(1): 9–19.
32 Kim YH, Bagot M, Pinter-Brown L et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018; 19(9): 1192–204.
33 Duarte RF, Canals C, Onida F et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sézary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010; 28(29): 4492–9.
34 Eberle FC, Holstein J, Scheu A et al. Intralesional anti-CD20 antibody for low-grade primary cutaneous B-cell lymphoma: Adverse reactions correlate with favorable clinical outcome. J Dtsch Dermatol Ges 2017; 15(3): 319–23.
35 Byrd JC, Flynn JM, Kipps TJ et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood 2016; 127(1): 79–86.
36 Fang C, Zhu D, Dong H et al. Lenalidomide alone or in combination with chemotherapy treatment for subtypes of diffuse large B cell lymphoma: a systematic review and meta-analysis. Int J Clin Exp Med 2015; 8(7): 10705–13.
37 Amber KT, Bloom R, Nouri K. Second primary malignancies in CTCL patients from 1992 to 2011: a SEER-based, population-based study evaluating time from CTCL diagnosis, age, sex, stage, and $CD30^+$ subtype. Am J Clin Dermatol 2016; 17(1): 71–7.
38 Smoller BR, Marcus R. Risk of secondary cutaneous malignancies in patients with long-standing mycosis fungoides. J Am Acad Dermatol 1994; 30(2 Pt 1): 201–4.
39 Brownell I, Etzel CJ, Yang DJ et al. Increased malignancy risk in the cutaneous T-cell lymphoma patient population. Clin Lymphoma Myeloma 2008; 8(2): 100–5.
40 Kim YJ, Shin HJ, Won CH et al. The incidence of other primary cancers in patients with cutaneous lymphoma. Ann Dermatol 2018; 30(3): 335–41.
41 Goyal A, O'Leary D, Goyal K et al. Increased risk of second primary hematologic and solid malignancies in patients with mycosis fungoides: a surveillance, epidemiology, and end results analysis. J Am Acad Dermatol 2020; 83(2): 404–11.
42 Stern RS, Study PF-U. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. J Am Acad Dermatol 2012; 66(4): 553–62.
43 Osman MM1, Altinyay ME, Abdelmalik AG et al. FDG PET/CT incidental diagnosis of a synchronous bladder cancer as a fourth malignancy in a patient with head and neck cancer. Clin Nucl Med 2011; 36(6): 496–7.

