

# Chapter 29

## Cutaneous Lymphomas

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**Abstract** Primary cutaneous lymphomas represent a group of lymphatic malignancies arising primarily in the skin. They represent the second most common form of extranodal non-Hodgkin lymphomas and are characterized by heterogeneous clinical, histological, immunological, and molecular features. Their variety reflects the complexity of the lymphocytic populations of the skin and the different levels of malignant transformation. They thus include primary cutaneous T-cell lymphomas, primary cutaneous B-cell lymphomas, and a rare cutaneous blastic plasmacytoid dendritic cell neoplasm. Most of the primary cutaneous lymphomas are indolent neoplasms, confined to the skin for a long period of time without significant influence on life expectancy and therefore do not require systemic therapy in the beginning. Systemic immunomodulatory treatment is generally reserved for advanced stages and tries to counteract Th2-skewing cytokine dysbalance or to target lymphoma T or B cells specifically.

**Keywords** Cutaneous lymphomas • Cutaneous T-cell lymphomas • Cutaneous B-cell lymphomas • Immune interventions

### 29.1 Introduction

Primary cutaneous lymphomas represent a heterogeneous and dynamic group of malignancies that derive from transformed immune cells in the skin. The first published description of a cutaneous lymphoma (mycosis fungoides) was made by Jean-Louis Alibert in the nineteenth century [5]. Since then it took almost 150 years to acknowledge primary cutaneous lymphomas as an independent entity. In 2005 published WHO-EORTC classification of primary cutaneous lymphomas reached an agreement for characteristic features of the different primary cutaneous

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lymphomas and other hematologic neoplasms that frequently manifest in the skin and provide a solid basis for diagnosis and treatment, which has led to its wide acceptance [66]. Based on WHO-EORTC classification, these rare lymphomas were also included in the recent fourth edition of WHO classification of tumors of hematopoietic and lymphoid tissues [56].

Primary cutaneous lymphomas represent the second most common form of extranodal non-Hodgkin lymphomas and are characterized by heterogeneous clinical, histological, immunological, and molecular features. Their variety reflects the complexity of the lymphocytic populations of the skin and the different levels of malignant transformation. By definition primary cutaneous lymphomas represent clonal accumulation of lymphocytes in the skin and include primary cutaneous T-cell lymphomas, primary cutaneous B-cell lymphomas, and a rare separate entity of cutaneous blastic plasmacytoid dendritic cell neoplasms [32, 56, 66]. An important distinction between primary and secondary cutaneous lymphoma is that the former are restricted to the skin at the time of initial diagnosis [66], whereas secondary cutaneous lymphomas have an obligatory extracutaneous origin with secondary involvement of the skin. Most of the primary cutaneous T- and B-cell lymphomas remain indolent and confined to the skin for a long period of time, not significantly influencing the overall survival and in the majority of cases not requiring systemic treatment [35, 55].

The goal of this chapter is to give an overview of the most common primary cutaneous lymphomas, focus on their immunological peculiarities, and discuss the possible therapy interventions targeting these immunological aspects.

## 29.2 Cutaneous T-Cell Lymphomas

Primary cutaneous T-cell lymphomas (CTCL) comprise a heterogeneous group of extranodal non-Hodgkin lymphomas with various clinical and histological manifestations that arise from malignant transformation of skin-homing T cells ( $CLA^+$ / $CCR4^+$ ) [22, 33, 66]. In a recent large study based on data from 13 institutions and a total of 6,230 CTCL cases, an overall annual CTCL incidence of approximately 7 new CTCL cases per million persons was calculated, and the total overall CTCL survival was 78.3 % [37].

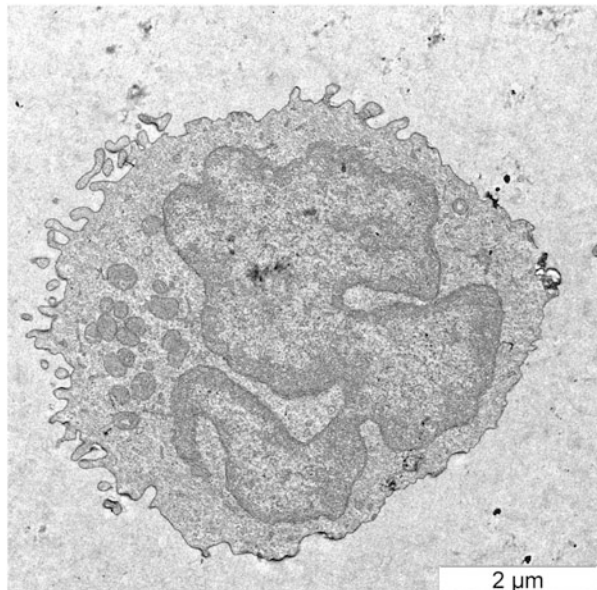
Mycosis fungoides (MF) is the most frequent one and accounts for approximately 60 % of all primary CTCL and for 1 % of all non-Hodgkin lymphomas [36]. Sézary syndrome (SS) is a less frequent erythrodermic and leukemic CTCL ( $\mu$ -CTCL) variant. Primary cutaneous CD30+ T-cell lymphoproliferative disorders (e.g., anaplastic large cell lymphoma and lymphomatoid papulosis) make up 20 % of CTCL. Three percent are comprised of other rare CTCL: subcutaneous panniculitis-like T-cell lymphoma ( $\alpha/\beta$  and  $\gamma/\delta$  subtype), extranodal NK/T-cell lymphoma, hydroa vacciniforme-like T-cell lymphoma, and the primary cutaneous peripheral T-cell lymphoma, not otherwise specified [50]. The WHO-EORTC (World Health Organisation-European Organization for Research and Treatment

of Cancer) classification of cutaneous T cell and NK/T cell lymphomas updated in 2005 gives an overview of the variety of primary CTCL [66].

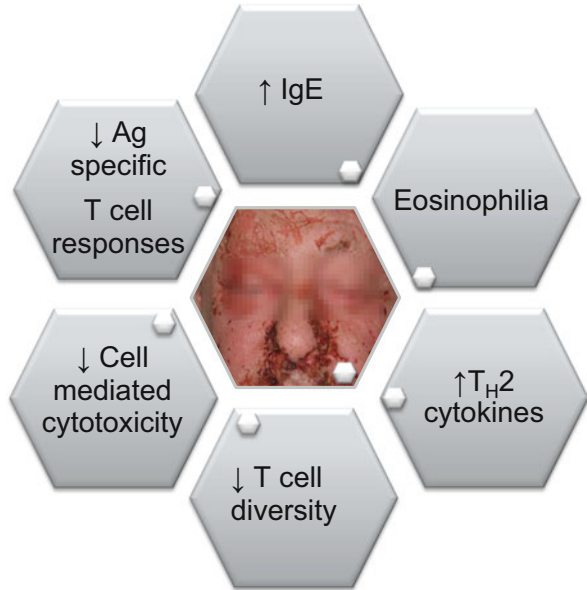
Although early-stage MF and SS have been considered to represent different stages in a disease continuum, differing molecular profiles and responses to therapy have provided new evidence that MF and SS may be distinct diseases [54]. Campbell, Clark, and colleagues recently suggested that the different clinical and biological behavior of SS and MF likely reflects the fact that the malignant T cells in these two CTCL variants arise from different memory T-cell subsets. Strong evidence indicates that malignant T cells in SS (leukemic CTCL) are of central memory T-cell phenotype ( $CD62L^+/CCR7^+$ ), which means that they actively recirculate through the skin, blood, and lymph nodes. This is consistent with the clinical presentation of SS with diffuse erythema of the skin, peripheral blood disease, and lymphadenopathy. Furthermore, T cells from MF skin lesions are of effector memory T-cell phenotype. Effector memory T cells are sessile in the skin and do not recirculate through the blood, and this would explain the tendency of MF plaques to remain in fixed anatomic locations for many years [6, 10].

Although likely of different biologic origin, MF and CTCL still share myriad common features. Malignant T cells in MF and SS are mostly  $CD4^+$  and only seldom  $CD8^+$  T helper cells with characteristic morphology. The cerebriform nuclei are their classical morphological hallmark and enable detection of malignant cells in blood smears and structurally well-preserved paraffin sections (Fig. 29.1). However, yet at a high-power magnification, CTCL cells are difficult to be detected via conventional laboratory methods. Clonality,  $CD158\kappa$  expression, or loss of  $CD26$  and/or  $CD7$  expression, as well as T-cell scatter profile on flow cytometry are characteristic of malignant T cells, however, a specific biomarker or specific

**Fig. 29.1** Electron microscopy of a malignant T cell in a patient with Sézary syndrome with characteristic prominent polychromatic cerebriform nucleus. Scale bar 2  $\mu$ m



**Fig. 29.2** Overview of immunological abnormalities in mycosis fungoides and Sézary syndrome patients



cell surface molecule that reliably identifies them has not yet been unequivocally defined [9, 15, 47].

From an immunological perspective, patients with MF and SS have clinical abnormalities characteristic of Th2 mediated immunologic processes, including decreased antigen-specific T-cell responses, impaired cell mediated cytotoxicity, peripheral eosinophilia, and elevated levels of serum IgE [46]. Notably, the malignant T cells themselves are the main source of extreme excess of Th2 cytokines, and further enforce a global Th2 bias and suppress protective Th1 responses in CTCL individuals [27].

Additionally, increased IL-31 production in malignant T cells has recently been described to correlate with CTCL pruritus [45]; other important cytokines such as IFN- $\gamma$ , IL-17, or TNF- $\alpha$  tend to be decreased, which likely accounts for the progressive impairment of cellular immunity and notorious susceptibility to infections in MF and SS individuals [33] (Fig. 29.2).

Activated dermal dendritic cells bridge innate and adaptive immune responses and are critical for tumor immune surveillance in the skin. Recently, Schwingshackl and colleagues analyzed the distribution and maturation status of different dendritic cell subsets in cutaneous lesions of MF and SS. Surprisingly, the numbers of dendritic cells are significantly increased within the skin infiltrate of both MF and CTCL; however, these dendritic cells are functionally largely immature. This phenomenon might be associated with induction of tumor tolerance or, on the contrary, may represent an on-going tumor immune surveillance [52]. Albeit critical observations on dendritic cells–T cells interactions in CTCL individuals are limited, activation status of the skin innate immune system might be a key factor for disease progression in CTCL [69, 70].

### 29.3 Cutaneous B-Cell Lymphomas

Primary cutaneous B-cell lymphomas (CBCL) are a heterogeneous group of lymphoproliferative disorders primarily arising in the skin that differ in biological behavior and prognosis [66]. The three most prevalent CBCL entities are part of the WHO classification of tumors of hematopoietic and lymphoid tissues as well as WHO-EORTC classification of cutaneous lymphomas: primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle-center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), which account for >90 % of CBCL [56, 66]. In contrast to cutaneous T-cell lymphomas that can affect large skin areas, CBCL mainly form circumscribed skin lesions, such as singular or multiple papules and nodules. Different types seem to favor different anatomic sites, such as the upper back and arms in PCMZL, head and neck region for PCFCL and lower legs in PCDLBCL-LT [24].

Both PCFCL and PCLBCL-LT are large B-cell lymphoma with yet significantly different clinical courses and prognoses. The five-year survival rate of PCFCL is 95 % [53], and that of PCDLBCL-LT is ~50 % emphasizing its aggressiveness [26, 66]. Tumor cells in PCDLBCL-LT are mainly centroblasts with few admixed reactive elements. Tumor cells in PCFCL consist of follicle center cells with predominantly centrocytic differentiation. PCFCL can have a follicular, follicular and diffuse, or diffuse growth pattern. In contrast to nodal and secondary cutaneous follicular lymphomas, they do not express *bcl-2* [8]. Gene expression profiling of PCFCL and PCDLBCL-LT revealed similarities to germinal center B-cell-like (GCB) and activated B-cell-like (ABC) nodal DLBCLs, respectively [29]. Likewise, immunohistochemical analysis could confirm overlaps between PCFCL and GCB [18, 71]. HGAL, B7-DC, MRC, CD130, and CXCR4, which are expressed in germinal center cells from normal tonsil were shown to be positive in PCFCL, but not in PCDLBCL-LT. On the other hand, most of PCLBCL-LT express MUM-1/IRF4 protein whereas PCFCL do not, which is associated with ABC nodal DLBCL [29]. Furthermore, PCDLBCL-LT also express cytoplasmic IgM with or without IgD in contrast to PCFCL. Array-based comparative genomic analysis also revealed differences in chromosomal alterations between PCFCL and PCDLBCL-LT [11].

PCMZL is a very indolent CBCL type with a 5-year disease-specific survival of almost 100 % [66]. Tumor cells of PCMZL consist of small B cells resembling marginal zone cells, lymphoplasmacytoid cells, and plasma cells. Characteristically, plasma cells can be observed particularly in the periphery of the tumor infiltrates. Neoplastic lymphocytes express B-cell markers (CD20, CD79a) and *bcl-2*, but are negative for CD5, CD10, and *bcl-6*. Infiltrating plasma cells typically display monoclonal expression of  $\kappa$ - and  $\lambda$ -Ig-light chains. The infiltrate may also include eosinophilic granulocytes, with moderate/marked tissue eosinophilia found almost only in Asian cases [58]. In the last WHO classification, PCMZL is assigned to the group of extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue (MALToma). However, PCMZL is distinguishable from other

extracutaneous MALTomas on various levels. Unlike other extranodal MALTomas, the translocations t(11;18) and t(14;18)(q32;q21) can be detected in only a small proportion of PCMZL. PCMZL express IgG, IgA, and IgE and thus differ from other extranodal MALTomas, which mostly express IgM. PCMZL with plasmacytic differentiation frequently express IgG4, whereas only 1 out of 120 noncutaneous marginal zone lymphomas expressed IgG4 [3]. Recently, PCMZL was recognized to encompass two subgroups [17, 64]. The more frequent one shows the presence of a class-switched immunoglobulin heavy chain and a distinct T-cell microenvironment with Th2-like cytokines opposite to Th1-like cytokines that characterize many extracutaneous MALTomas. In this subgroup, PCMZL are distinctive because the B cells frequently lack expression of CXCR3, a receptor for interferon- $\gamma$ -induced chemokines, usually present on activated T cells. If PCMZL are nevertheless expressing CXCR3, they also express IgM and are in some cases associated with *Borrelia burgdorferi* infection [17].

An association with *Borrelia burgdorferi* infection and CBCL development has been reported in European cases [25, 38], which has certain parallels to *Helicobacter pylori*-associated MALTomas of the gastrointestinal tract [20]. Large geographic differences appear to exist, as an association with a *Borrelia* infection has not been observed in all European countries [48], the United States [68], and Asia [41]. On the other hand, Bahler et al. analyzed the immunoglobulin heavy chain variable genes from eight US cases of PCMZL and found the usage of V(H) genes and motifs that suggest antigen triggering as growth stimulator [1]. Furthermore, numerous CD3+ T cells and CD123+ plasmacytoid dendritic cells were described in PCMZL implying antigen presence [39]. Clusters of CD123+ plasmacytoid dendritic cells (PDC) are observed in all PCMZL and the majority of cutaneous B-cell pseudolymphomas and minority of PCFCL, whereas PCDLBCL-LT were negative. Although the role of PDC in PCMZL remains unclear, the high number of PDC may indicate an infectious cause or cross-reacting autoantigens as the primary trigger for PCMZL, as PDC migrate to nonlymphoid tissues in response to inflammatory or infectious stimuli. These findings indicate that a clonally restricted response to chronic antigenic stimulation could play a role in the pathogenesis of PCMZL [39].

Similar to cutaneous T-cell lymphomas (CTCL), a significantly increased number of mast cells is observed in CBCL lesions and those infiltrations are correlated with disease progression [51]. BCA-1 (CXCL-13) and its receptor CXCR5 are constantly expressed in CBCL, but not in healthy skin and CTCL. BCA-1 is also expressed in B-cell pseudolymphoma, and its expression pattern differs between CBCL and B-cell pseudolymphoma. BCA-1 expression is restricted to CD22+ B-cells in CBCL, whereas BCA-1 is expressed in CD35+ dendritic cells in B-cell pseudolymphoma [44]. Expression of programmed death-1 (PD-1) on T cells appears to have prognostic significance in some types of nodal B cell lymphomas [7]. Recently, PD-1 expression, restricted to tumor infiltrating T cells (TILs), was also shown in CBCL [43]. It appears that PCMZL and PCFCL harbor higher numbers of PD-1 positive TILs than PCDLBCL-LT, which in turn may also reflect better prognosis of the former. These data are in line with gene expression profiling

studies on nodal follicle center lymphoma describing a more favorable clinical outcome in patients with a T-cell activation or subgroup signature [23].

In conclusion, CBCL represent a highly heterogeneous disease group that reflects morphologic and functional diversity of B-cells homing into the skin arising after malignant transformation.

## 29.4 Immunologic Therapeutic Interventions in Cutaneous Lymphomas

In the last decade, immense progress has been made in the biological therapy of primary cutaneous T- (CTCL) and B-cell (CBCL) lymphomas. It is, however, important to note that the majority of cutaneous lymphomas (CL) has an indolent nature and thus does not require aggressive treatment at the beginning. Studies have shown that early aggressive therapies do not improve the prognosis of patients with CTCL as compared with conservative treatment of topical therapies [31]. These and other data have led to a paradigm change in the therapy of CL, where cytotoxic therapies are not used as first-line treatment of indolent CL types. In early stages, the quality of life can be significantly impaired because of cosmetic concerns and itch, whereas advanced stages are often accompanied by immune dysfunctions leading to increased risk of infection and secondary malignancies. Hence, modern therapy algorithms consider the disease stage in order to achieve the best possible, sustainable, and life quality-preserving remission while reducing toxicity.

The simplest immunomodulatory skin-directed approach for CL lesions limited to the skin encompasses intermediate- and high-potency topical corticosteroids, with potency adapted to the infiltration of the lesion [2, 49]. Topically applied corticosteroids exert a multitude of inhibitory effects on both T and B cells which are well known [57] and result in efficient regression of skin lesions of different CL. Phototherapy is another effective skin-directed modality in the treatment of CTCL. Narrow-band ultraviolet B (UVB) light with a wavelength of 311 nm is becoming more popular over psoralen and UVA (PUVA) therapy, as it requires no premedication with photosensitizing psoralen and has fewer side effects, especially in terms of photoaging and UV-associated carcinogenesis. Apart from induction of multiple immunomodulatory molecules, UVB light induces DNA damage with changes in the cell cycle leading to lymphocyte apoptosis [4]. PUVA, on the other hand, not only downregulates expression of skin-homing molecules of epidermotropic malignant T-cells; it is far more potent than UVB in inducing apoptosis of T-lymphocytes in the skin. Although both therapies can be employed with equal success, narrow-band UVB appears to be superior in cases with limited disease [2, 67]. A further development in the field of topical immunomodulators is imiquimod, a small molecule compound that activates Toll-like receptor (TLR) 7 and induces production of myriad pro-inflammatory cytokines [12]. By activating plasmacytoid dendritic cells that express TLR7, imiquimod activates cytokine



production, dominated by interferon (IFN)  $\alpha$ , which counteract immune dysbalance in different CL types and promote antitumor immunity [61]. This effect could be potentiated by immunostimulatory activity of the isostearic acid, a major component of its cream vehicle [65].

Systemic immunomodulatory treatment is reserved for advanced stages or for therapy-resistant lymphoma lesions. For this purpose, various recombinant Th1-skewing cytokines, such as IFN- $\alpha$  and IFN- $\gamma$  are currently routinely used either via intralesional or systemic route to treat these lymphomas [2, 12, 19, 67]. The goal is to reverse lymphoma-induced Th2-potentiated immunosuppression thereby stimulating antitumor immune effectors. To circumvent systemic toxicities, which can be a limiting factor in the treatment with IFNs, an adenovirus containing a human IFN- $\gamma$  gene was constructed and tested for intralesional application in various CLs, showing overall good tolerability and higher response rates in CBCL than in CTCL [14, 16, 60]. Interestingly, patients who fail to respond to IFN-based treatments appear to have “IFN resistance,” that is, defects in the IFN signaling pathway [61, 62]. These defects can be successfully targeted by replicating measles virus that easily lyses lymphoma cells (i.e., oncolytic virus therapy) as they are no longer able to mount an efficient antiviral response [13, 28]. TLR stimulation can also be achieved systemically by employing oligonucleotide CpG-7909 that acts as a TLR9 agonist and induces a similar plethora of cytokines as imiquimod. Promising results have been shown in CTCL patients [34], and further studies are on the way not only in T- but also in B-cell malignancies [40]. In advanced stages of CTCL with leukemic blood involvement, extracorporeal photopheresis (ECP) can be used alone or combined with IFN- $\alpha$ . ECP is a method where circulating mononuclear cells are separated by a leukapheresis-based technique, mixed with psoralen and reinfused to the patient. This therapy option, representing PUVA treatment of blood, is thought to induce apoptosis of circulating malignant lymphocytes and to stimulate antitumor response through release of tumor antigens and generation of dendritic cells from monocytes [67].

Development of monoclonal antibodies (mAbs) targeting surface molecules on T and B cells is a fast growing addition to the repertoire of immunotherapeutic options in CL. In CTCL, targeting CD4 by zanolimumab and CD52 by alemtuzumab shows variable success depending on the lymphoma type treated [2]. Denileukin–diftitox is a fusion protein, which consists of diphtheria toxin fragments conjugated to interleukin 2. After binding to interleukin-2–receptor this molecule is internalized, where it leads to inhibition of protein synthesis and apoptosis [21]. Its activity as a single agent or in combination with chemotherapy has been shown in CTCL patients who are CD25 positive [30]. Brentuximab–vendotin is a conjugate of an antibody against CD30 with methyl-aurostatin E, a tubulin destabilizing agent, that can be selectively used for CD30+ CL [63].

In CBCL, expression of CD20 is mandatory for the treatment with rituximab, a human–mouse chimeric antibody against CD20. Rituximab can be used either via an intralesional or systemic route and has shown impressive responses in CBCL [19]. Anti-CD20 antibodies can also be conjugated with various radionuclides, such as yttrium ( $^{90}\text{Y}$ -ibritumomab tiuxetan) or iodine ( $^{131}\text{I}$ -tositumomab) and applied



with or without chemotherapy in relapsed patients or patients with refractory disease [59]. Several additional antibodies targeting other molecules on B cells, such as CD22 (epratuzumab), CD19 (Medi-551), and their toxin conjugates inotuzumab-ozogamicin (CD22) and SAR3419 (CD19) come from the field of nodal lymphomas and may be of interest in CBCL. Bispecific T-cell-engager molecules, also known as BiTEs, are another novelty and represent single-chain dual-specific antibodies that target both CD3 on the surface of T cells and a specific antigen on the surface of the malignant B cell in order to induce cell lysis. One BiTE with specificity to CD19, blinatumomab (MEDI-538), has demonstrated high clinical activity in B-cell leukemia and lymphoma patients [59].

Lastly, it should not be left unsaid that not only immunotherapeutics are engaged in immune modulation, but also other compounds used for CL, such as histone deacetylase inhibitors, may have profound immunomodulatory properties through regulation of innate and adaptive immune responses [42]. If all therapies fail, allogeneic stem cell transplantation may become the last resort, particularly in CTCL, inasmuch as autologous stem cell transplantation has yielded disappointing results. Immune interventions in CL have and are working well, emphasizing strong immunogenicity of these tumors and giving hope that the time will come where a therapeutic intervention will not only stabilize but be able to cure the disease.

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