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XV. Primary cutaneous lymphomas

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introduction

Primary cutaneous lymphomas (PCLs) are defined as non-Hodgkin lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. After the gastrointestinal lymphomas, PCL are the second most common group of extranodal non-Hodgkin lymphomas with an estimated annual incidence of 1/100 000. These PCLs must be distinguished from nodal or systemic malignant lymphomas involving the skin secondarily, which often have another clinical behavior, have a different prognosis and require a different therapeutic approach. In recent lymphoma classifications (WHO-EORTC; WHO 2008) the different types of primary cutaneous T-cell lymphoma (CTCL) and primary cutaneous B-cell lymphoma (CBCL) are therefore included as separate entities (see Table 1) [1, 2]. In the western world, CTCL constitutes ∼75%–80% of all PCLs and CBCL 20%–25%, but different distributions have been observed in other parts of the world. Within the group of CTCLs roughly three categories can be distinguished: (i) the group of classical CTCLs, including mycosis fungoides (MF), variants or subtypes of MF and Sézary syndrome (SS); (ii) the group of primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD); and (iii) a group of rare often aggressive cutaneous T/NK-cell lymphomas, including subcutaneous panniculitis-like T-cell lymphoma (SPTCL), extranodal NK/T-cell lymphoma, nasal type, and primary cutaneous peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Well-defined types of CBCL include primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT).

Herein, characteristic features of the main types of CTCL and CBCL are summarized and recent observations regarding diagnosis, prognostic factors and treatment are described.

mycosis fungoides

MF is the most common type of CTCL and accounts for ∼65% of all CTCL. Characteristically, patients with classical MF present with patches and plaques and most patients never progress beyond the plaque stage of disease. However, in a number of patients progression may occur with the development of nodules or tumors and involvement of nodal and/or visceral sites. The prognosis of patients with MF is above all dependent on the stage of the disease [3]. In particular, the presence of effaced lymph nodes, visceral involvement and transformation into a large T-cell lymphoma, defined by the presence of >25% blast cells in the dermal infiltrate, are considered risk factors for an aggressive clinical course. However, in a study including 100 patients with transformed MF no significant difference in survival was found between patients with tumor stage MF with or without large cell transformation. In the same study patients with transformed MF expressing CD30 had a significantly better prognosis than CD30-negative cases (M. F. Benner, unpublished)

Since early aggressive chemotherapy is associated with considerable side-effects, but does not improve survival, a stage-adapted conservative therapeutic approach is recommended for MF. In patients with early stage MF (stage IA–IIA) skin-directed therapies including topical steroids, photo(chemo)therapy and topical cytostatic agents, such as mechlorethamine or carmustine (BCNU), can be used. In patients developing one or few tumors (stage IIB) additional local radiotherapy suffices. Patients with more extensive plaques and tumors or patients refractory to abovementioned therapies a combination of psoralen plus ultraviolet A (PUVA) and interferon or PUVA and retinoids or rexinoids, or total skin electron beam irradiation can be considered. In patients with advanced and refractory disease a rapidly growing list of new therapies have become available [4]. These include among others histone deacetylase (HDAC) inhibitors, the fusion toxin denileukin diftitox, praletraxate, Toll-like receptor agonists, gemcitabine and liposomal doxorubicin. The response rates of most of the biological agents vary between 25% and 35%, and the exact place of these new drugs in the treatment of MF, either alone or in combination with other treatment modalities, has still to be defined. Multi-agent chemotherapy is only indicated in patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumor stage MF which cannot be controlled with skin-targeted and immunomodulating therapies. Recent studies suggest that allogeneic hematopoietic stem cell transplantation can be an effective alternative in selected patients with advanced MF and SS [5].

Sézary syndrome

Sézary syndrome (SS) is defined historically by the triad of erythroderma, generalized lymphadenopathy and the presence of clonal neoplastic T cells (Sézary cells) in the skin, lymph nodes and peripheral blood. The prognosis of patients with SS is generally poor, with an overall 5-year-survival of ∼25%.

Table 1. PCLs in the WHO-EORTC and WHO 2008 classifications

Cutaneous T-cell lymphoma
Mycosis fungoides (MF)
Variants of MF
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Primary cutaneous CD30-positive lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal-type
Primary cutaneous peripheral T-cell lymphoma, NOS
Aggressive epidermotropic CD8+ CTCL[a]
Cutaneous γδ T-cell lymphoma
CD4+ small/medium-sized pleomorphic CTCL[a]
Cutaneous B-cell lymphoma
Primary cutaneous marginal zone B-cell lymphoma[b]
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type

[a]Provisional entities.
[b]In the WHO 2008 classification included in the group of extranodal MALT lymphomas.

Most patients die of opportunistic infections due to immunosuppression. Being a systemic disease (leukemia) by definition, systemic treatment is required. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities, has been suggested as the treatment of choice in SS, with overall response rates of 30%–80%, or complete response rates of 14%–25%. However, the suggested superiority of ECP over the traditional low-dose chemotherapy regimens has not yet been substantiated by controlled randomized trials. Prolonged treatment with a combination of low-dose chlorambucil and prednisone, bexarotene, denileukin diftitox, (low-dose) alemtuzumab and multi-agent chemotherapy have been recommended as second-line treatment of SS [6].

The relationship between SS and MF is a matter of ongoing debate. In past decades the view that SS is a leukemic variant of MF or a leukemic phase of CTCL prevailed. However, recent studies demonstrated that the malignant cells in SS are derived from central memory T cells, while the malignant cells in MF express markers of skin-resident effector memory T cells [7]. These observations suggest that MF and SS should be considered as separate entities derived from distinct functional T-cell subsets. In addition, recent molecular genetic studies showed major differences between MF and SS, which not only suggest a different molecular pathogenesis, but would also imply that MF and SS should not be lumped together in clinical trials [8].

primary cutaneous CD30-positive lymphoproliferative disorders

Primary cutaneous CD30-positive lymphoproliferative disorders represent the second most common group of CTCL, accounting for ~25% of CTCL. This group includes primary cutaneous anaplastic large cell lymphoma (C-ALCL) and lymphomatoid papulosis (LyP), which have overlapping clinical, histological and immunophenotypical features and form a spectrum of diseases [1, 2].

C-ALCLs generally present with solitary or localized nodules or tumors that often develop ulceration, and have a tendency to regress spontaneously. These lymphomas frequently relapse in the skin, but extracutaneous dissemination, which mainly involves regional lymph nodes, is uncommon. The prognosis of C-ALCL is usually favorable with a 10-year disease-related survival exceeding 85% [9]. Recent studies suggest that patients presenting with extensive limb involvement have a more unfavorable prognosis [10, 11]. Unlike systemic ALCL, C-ALCLs do not express anaplastic lymphoma kinase (ALK) and are not associated with the t(2;5) chromosomal translocation. Rare ALK-1-positive cases presenting with only skin lesions should be considered and treated as systemic ALCL. Recent molecular genetic studies suggest that increased espression of skin-homing chemokine receptors and CD30-mediated NF-κB activation play an important role in the pathogenesis of C-ALCL [12].

C-ALCL presenting with solitary or localized lesions should be treated with radiotherapy or surgical excision. Patients presenting with multifocal skin lesions can best be treated with radiotherapy in the case of only a few lesions, or with low-dose methotrexate as in LyP. Multi-agent chemotherapy is only indicated in patients presenting with or developing extracutaneous disease and rare patients with rapidly progressive skin disease [9].

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was originally defined as a cytotoxic T-cell lymphoma, which preferentially infiltrates the subcutaneous tissue, and is associated with an aggressive clinical behavior requiring aggressive multi-agent chemotherapy.

In recent classifications the term SPTCL is only used for cases with an αβ T-cell phenotype, while cases expressing the γδ T-cell receptor are reclassified as primary cutaneous γδ T-cell lymphoma (PCGD-TCL). SPTCL occurs in adults as well as in young children. Patients generally present with solitary or multiple nodules or deeply seated plaques, which mainly involve the legs, the arms and the trunk. Ulceration is uncommon. Systemic symptoms such as fever, fatigue and weight loss, and laboratory abnormalities, including cytopenias and elevated liver function tests are common, but a frank hemophagocytic syndrome (HPS) is observed in only 15% of patients [13]. Dissemination to extracutaneous sites is rare. SPTCL has an excellent prognosis particularly if not associated with a HPS. A recent study reports 5-year overall survival of 91% and 46% in SPTCL patients without and with a HPS, respectively [13]. In SPTCL without associated HPS systemic steroids or other immunosuppressive agents are recommended, whereas in cases of solitary skin lesions radiotherapy is advised. Only in cases with progressive disease not responding to immunosuppressive therapy and

in cases with HPS should multi-agent chemotherapy be considered.

primary cutaneous peripheral T-cell lymphoma, not otherwise specified

The designation PTCL-NOS is maintained for cutaneous T-cell lymphomas that do not fit into any of the better defined subtypes of CTCL, and is thus a diagnosis of exclusion. The prognosis is generally poor with 5-year survival rates of <20%. Patients are commonly treated with multi-agent chemotherapy, but the results are often disappointing. Histologically, PTCL-NOS show nodular or diffuse infiltrates with variable numbers of medium-sized to large pleomorphic or immunoblast-like T cells, and may be indistinguishable from tumor stage MF. In particular, when confined to the skin patients with tumor stage have a much better prognosis and should be treated primarily with skin-targeted therapies and not with multi-agent chemotherapy. Thus, in all cases with a histologic diagnosis of PTCL-NOS a diagnosis of MF must be ruled out by complete clinical examination and an accurate clinical history.

Within the group of primary cutaneous PTCL-NOS three somewhat better defined subgroups have been delineated. These include primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, primary cutaneous γδ T-cell lymphoma (PCGD-TCL) and primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma (see Table 1).

primary cutaneous γδ T-cell lymphoma

PCGD-TCL is a lymphoma composed of a clonal proliferation of mature, activated γδ T cells with a cytotoxic phenotype. This group includes cases previously known as SPTCL with a γδ phenotype. PCGD-TCL generally presents with disseminated plaques and/or ulceronecrotic nodules or tumors. Involvement of mucosal and other extranodal sites is frequently observed, but involvement of lymph nodes or bone marrow is uncommon. PCGD-TCLs are resistant to multi-agent chemotherapy and have a poor prognosis [1, 2, 13].

primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma

These lymphomas are characterized by a proliferation of epidermotropic CD8-positive cytotoxic T cells and an aggressive clinical behavior. Clinically, they show localized or disseminated eruptive papules, nodules and tumors showing central ulceration or superficial, hyperkeratotic patches and plaques. Similar to PCGD-TCL, these lymphomas may disseminate to mucosal and other extranodal sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared. These lymphomas also run an aggressive clinical course.

These aggressive CD8-positive cytotoxic CTCLs should be distinguished from cases of classical MF with a CD8+ T-cell phenotype, which have the same clinical behavior and prognosis as CD4-positive MF cases, and from a recently defined entity designated indolent CD8-positive lymphoid proliferation of the ear [14]. This term has been used for cases presenting with a slowly progressive nodule on the ear (or nose), which combine an indolent clinical course with histologic features suggesting a high-grade malignant lymphoma with a CD3+, CD4–, CD8+, TIA-1+, granzyme B–, CD30– T-cell phenotype. Loss of pan-T-cell antigens and the presence of clonal T-cell receptor gene rearrangements provide further support for the malignant nature of this condition. However, the proliferation rate is generally low. Recognition that these patients have an indolent clinical course, despite an aggressive histology, should prevent unnecessarily aggressive treatment.

primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma

Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL) is defined by a predominance of small to medium-sized CD4-positive pleomorphic T- cells without (a history of) patches and plaques typical of MF. Characteristically, these lymphomas present with a solitary plaque or tumor, generally on the face, the neck or the upper trunk. Less commonly, they present with generalized skin lesions. Characteristic histological features include an infiltrate of CD4-positive small/medium-sized pleomorphic T cells, admixed with a small proportion (<30%) of large pleomorphic T cells, often a considerable admixture with reactive CD8+ T cells, B cells, plasma cells and histiocytes, and a low proliferation rate. These features are very similar to those described for so-called pseudo-T-cell lymphomas in the past, but nowadays most investigators use the presence of T-cell clone as a useful criterion for PCSM-TCL.

Patients presenting with a solitary lesion, which can easily be treated with excision or local radiotherapy, have an excellent prognosis. Patients with rapidly evolving large tumors, a high proliferation index and few admixed CD8+ T cells may run a more aggressive clinical course [15]. Recognition of this entity, separate from other primary cutaneous PTCL-NOS, is important to avoid unnecessarily aggressive treatment of these patients.

cutaneous B-cell lymphoma

In recent classifications three main types of CBCL are distinguished: primary cutaneous marginal zone lymphoma (PCMZL), PCFCL and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT). PCMZL and PCFCL are indolent types of CBCL with disease-related 10-year survival exceeding 90%, while PCLBCL-LT has a more unfavorable prognosis (disease-related 5-year survival, ~50%). Recently, EORTC/ISCL consensus recommendations for the management of these three types of CBCL have been formulated, which are summarized in Table 2 [16].

Table 2. Recommendations for the initial management of CBCL [16]

	Extent	First line therapy	Alternative therapies
PCMZL	Solitary/localized	Local radiotherapy	IFN-α i.l.
		Excision	Rituximab i.l.
		(Antibiotics)[a]	i.l. steroids
	Multifocal	Wait-and-see	IFNα i.l.
		Local radiotherapy	Rituximab i.l.
		Chlorambucil[b]	Topical or i.l. steroids
		Rituximab i.v	
		(Antibiotics)[a]	
PCFCL	Solitary/localized	Local radiotherapy	IFN-α i.l.
		Excision	Rituximab i.l.
	Multifocal	Wait-and-see·	R-CVP/CHOP [c]
		Local radiotherapy	
		Rituximab i.v.	
			Rituximab i.v.
PCLBCL, LT	Solitary/localized	R-CHOP +/– IFRT	Local radiotherapy
	Multifocal	R-CHOP	Rituximab i.v.

[a]In the case of evidence of *Borrelia burgdorferi* infection.
[b]Or other single or combination regimens appropriate for low-grade B-cell lymphomas.
[c]In exceptional cases or for patients developing extracutaneous disease.
i.l., intralesional; i.v., intravenous; IFRT, involved field radiotherapy.

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