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Prognostic factors in cutaneous T-cell lymphoma

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The term cutaneous T-cell lymphoma (CTCL) describes a heterogeneous group of neoplasms of skin-homing T cells that show considerable variation in clinical presentation, histological appearance, immunophenotype and prognosis. CTCL represent approximately 75-80% of all primary cutaneous lymphomas, whereas primary cutaneous B-cell lymphomas (CBCL) account for approximately 20-25%.[1] For many years mycosis fungoides (MF) and Sézary's syndrome (SS) were the only known types of CTCL. In the last decade, based on a combination of clinical, histological and immunophenotypical criteria, new types of CTCL have been defined, and included in new classifications for (primary cutaneous) malignant lymphomas, such as the EORTC classification,[1] the WHO classification,[2] and most recently the new WHO-EORTC classification for cutaneous lymphomas (Table 1).[3] In the WHO-EORTC classification roughly three categories of CTCL can be distinguished:[1] the group of classical CTCL, including MF, variants or subtypes of MF and SS;[2] the group of primary cutaneous $CD30^+$ lymphoproliferative disorders ($CD30^+$ LPD); and[3] a group of rare often aggressive cutaneous T/NK cell lymphomas, including subcutaneous panniculitis-like T-cell lymphoma (SPTL), extranodal NK/T-cell lymphoma, nasal type, and cutaneous peripheral T-cell lymphoma (PTL), unspecified. In this latter group, aggressive epidermotropic CD8-positive CTCL, cutaneous γ/δ T-cell lymphoma (CGD-TCL) and primary cutaneous CD4-positive small-medium pleomorphic T-cell lymphoma have been separated out as provisional entities.[3] Classification according to the WHO-EORTC classification is the most important prognostic factor and a prerequisite for adequate management and treatment of these conditions. Herein, characteristic features of the different types of CTCL are described and prognostic factors within these categories are discussed.

Mycosis fungoides

Mycosis fungoides (MF) represents the most common type of CTCL and accounts for approximately 50% of all primary cutaneous lymphomas (Table 1). Characteristically, patients with classical MF present with patches and plaques which have a predilection for the buttocks and other covered sites of the trunk. It should be stressed that many 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. Histologically, early patch/plaque lesions are characterized by infiltration of the epidermis with atypical T-cells with small, medium-sized, or large highly convoluted (cerebriform) and sometimes hyperchromatic nuclei (epidermotropism). The neoplastic cells have the phenotype of mature skin homing $CD3^+$, $CD4^+$, $CD45RO^+$, $CD8^-$ memory T-cells. With progression to tumor stage the dermal infiltrates can involve the entire dermis and extend into the subcutaneous tissue. Epidermotropism may no longer be present. The tumor cells increase in number and size, showing variable proportions of small, medium-sized or large cells with cerebriform nuclei, blast cells with prominent nuclei and intermediate forms.

Prognostic features

Most patients with MF run an indolent clinical course over years or even decades. The prognosis of patients with MF is dependent on the stage, and in particular the type and extent of skin lesions and the presence of extracutaneous disease.[4,5] Patients with limited

Table 1. WHO-EORTC classification for cutaneous T-cell lymphomas.

Classical types of CTCL (ca. 65%)
Mycosis fungoides
Mycosis fungoides variants and subtypes
- Folliculotropic MF
- Pagetoid reticulosis
- Granulomatous slack skin
Sézary syndrome
Primary cutaneous CD30-positive lymphoproliferative disorders (ca. 25%)
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Rare types of CTCL (<10%)
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal-type
Primary cutaneous peripheral T-cell lymphoma, unspecified
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma
- Cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma

patch/plaque stage MF have a similar long-term life expectancy as an age-, sex-, and race-matched control population. In a study of 309 Dutch MF patients the disease-related 10-year survival of patients with limited patch/plaque disease, generalized patch/plaque disease and tumor stage disease without concurrent lymph node involvement were 97%, 83% and 42%, respectively, but only 20% for patients with histologically documented lymph node involvement.[5] Risk factors associated with an aggressive clinical course include the presence of effaced lymph nodes, visceral involvement, and transformation into a large T-cell lymphoma.[6] Follicultropic MF is a distinct variant of MF, characterized by the presence of folliculotropic infiltrates, often with sparing of the epidermis and preferential involvement of the head and neck region. Because of the deep (peri)follicular localization of the neoplastic infiltrates the skin lesions are less accessible to skin-targeted therapies. Consistently, the survival of patients with folliculotropic MF is more unfavorable than classical MF.[7]

Sézary's syndrome

Sézary's syndrome (SS) is defined historically by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes and peripheral blood. Criteria recommended for the diagnosis of SS include demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods, in combination with immunophenotypical abnormalities (an expanded $CD4^+$ T-cell population resulting in a CD4/CD8 ratio more than 10 and/or aberrant expression of pan-T-cell antigens) and an absolute Sézary cell count of least 1000 cells per mm^3.[3]

Prognostic factors

The prognosis of patients with SS is generally poor, with an overall 5-year-survival of approximately 25%. Most patients die of opportunistic infections due to immunosuppression. High absolute Sézary cell counts, and high levels of LDH and β-2-microglobulin have been reported as poor prognostic factors.[8]

Primary cutaneous CD30-positive lymphoproliferative disorders

Primary cutaneous CD30-positive lymphoproliferative disorders represent the second most common group of CTCL, accounting for approximately 25% of CTCL. This group includes primary cutaneous anaplastic large cell lymphoma (C-ALCL), lymphomatoid papulosis (LyP), and borderline cases. C-ALCL and LyP have overlapping clinical, histological and immunophenotypical features and form a spectrum of diseases.[3]

Clinically, C-ALCL generally present with solitary or localized nodules or tumors that often develop ulceration. Multifocal lesions are seen in about 20% of the patients. The skin lesions may show partial or complete spontaneous regression, as in LyP. These lymphomas frequently relapse in the skin. Extracutaneous dissemination occurs in approximately 10% of the patients, and mainly involves the regional lymph nodes. LyP is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a (CD30-positive) malignant lymphoma. The typical skin lesions in LyP are red-brown papules and nodules that may develop central hemorrhage, necrosis and crusting, and subsequently spontaneously disappear within 3 to 12 weeks. The number of lesions may vary from several to more than one hundred. Histologically, the conditions within this spectrum show a proliferation of large $CD30^+$ T-cells with an anaplastic or pleomorphic morphology, with a variable admixture of inflammatory cells. Whereas C-ALC how cohesive sheets of large $CD30^+$ tumor cells with relatively few admixed inflammatory cells, LyP lesions often show an abundant inflammatory infiltrate with relatively few large $CD30^+$ T-cells. However, overlapping features exist and it is generally accepted that differentiation between both

Table 2. Characteristics and subdivision of subcutaneous panniculitis-like T-cell lymphoma (SPTL).

WHO classification	*SPTL (α/β T-cell)*	*SPTL (γ/δ T-cell)*
Phenotype	TCRbeta1+; CD4-, CD8+, CD56-	TCRdelta-1+ CD4-, CD8-, CD56+
Architecture	subcutaneous	Subcutaneous and (epi)dermal
Hemaphagocytic syndrome	rare	Frequent
5-year-survival	80%	<10%
Treatment	Systemic steroids; Systemic chemotherapy	Systemic chemotherapy
WHO-EORTC classification	SPTL	CGD-TCL

CGD-TCL: cutaneous gamma/delta T- cell lymphoma.

conditions is not possible on the basis of histology alone, but ultimately depends on the clinical presentation and clinical behaviour. The $CD30^+$ neoplastic cells often express a $CD4^+$ T-cell phenotype with variable loss of CD2, CD5 and/or CD3. Expression of cytotoxic proteins (granzyme B, TIA-1, perforin) is noted in approximately 70% of the cases. Unlike systemic $CD30^+$ lymphomas, most primary cutaneous $CD30^+$ large T-cell lymphomas express the cutaneous lymphocyte antigen (CLA), but do not express EMA and ALK (anaplastic lymphoma kinase) and is not associated with the t(2;5) chromosomal translocation.

Prognosis and prognostic features

The prognosis of C-ALCL is usually favorable with a 10-year disease-related survival exceeding 85%.[9,10] Patients presenting with multifocal lesions and patients with involvement of only regional lymph nodes have a similar prognosis to patients with only skin lesions.[9] LyP also has an excellent prognosis. In a recent study of 118 patients only 5 (4%) patients developed a systemic lymphoma, and only 2 (2%) patients died of systemic disease over a median follow-up period of 77 months.[9] Risk factors for the development of systemic lymphoma are unknown.

Subcutaneous panniculitis-like T-cell lymphoma

In the WHO classification subcutaneous panniculitis-like T-cell lymphoma (SPTL) is defined as a cytotoxic T-cell lymphoma characterized by the presence of primarily subcutaneous infiltrates of small, medium-sized or large pleomorphic T-cells and many macrophages, predominantly affecting the legs, and often complicated by a hemophagocytic syndrome.[2] Rimming of individual fat cells by neoplastic T-cells is a helpful though not entirely specific diagnostic feature. Necrosis, karyorrhexis and cytophagocytosis are com¬mon findings. SPTL as defined in the WHO classification include cases with an α/β T-cell phenotype (75%) and cases with a γ/δ T-cell phenotype (25%). Patients should be treated with systemic chemotherapy and the prognosis is considered poor.

Prognosis and prognostic features

Recent studies have shown both clinical, histological and immunophenotypical differences between cases of SPTL with an α/β T-cell phenotype and those with a γ/δ T-cell phenotype, suggesting that these may represent different entities (see Table 2). SPTL with an α/β T-cell phenotype often have a protracted clinical course with recurrent subcutaneous lesions but without extracutaneous dissemination or the development of a hemophagocytic syndrome, and have a 5-year-survival of approximately 80%.[11] In contrast, SPLTL with a γ/δ T-cell phenotype overlap with other types of γ/δ-positive T-cell lymphoma and invariably run a very aggressive clinical course.[12] In the WHO-EORTC classification the term SPTL is only used for cases with an α/β^+ T-cell phenotype, whereas cases with a γ/δ^+ T-cell phenotype are included in the group of cutaneous γ/δ T-cell lymphomas (CGD-TCL), which is included as a provisional entity in the broad category of peripheral T-cell lymphoma, unspecified.[3] It should be emphasized that this new subdivision is based on reports of small number of patients and still needs further confirmation.

Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type is a nearly always EBV positive lymphoma with a NK-cell, or more rarely a cytotoxic T-cell phenotype. The skin is the second most common site of involvement after the nasal cavity/nasopharynx, and skin involvement may be a primary or secondary manifestation of the disease. This condition is

rare in Europe and the US, and more common in Asia, Central America and South America. Patients generally present with multiple plaques or tumors preferentially on the trunk and extremities, or in case of nasal NK/T-cell lymphoma with a midfacial destructive tumor, previously also designated lethal midline granuloma. Ulceration is common. Histologically, these lymphomas show dense infiltrates of small, medium-sized and/or large tumor cells, and prominent angiocentricity and angiodestruction, which is often accompanied by extensive necrosis. The neoplastic cells express CD2, CD56, cytoplasmic CD3ε and cytotoxic proteins (TIA-1, granzyme B, perforin), but lack surface CD3. In rare CD56 negative cases detection of EBV by in-situ-hybridization and expression of cytotoxic proteins are required for diagnosis.

Prognosis and prognostic features

Nasal type NK/T-cell lymphoma presenting in the skin is a highly aggressive tumour with a median survival of less than 12 months.[13,14] The most important factor predicting poor outcome is the presence of extracutaneous involvement at presentation. In patients presenting with only skin lesions a median survival of 27 months was reported, compared to 5 months for patients presenting with cutaneous and extracutaneous disease.[14] $CD30^+$, $CD56^+$ cases reported to have a better prognosis may have been examples of C-ALCL with co-expression of CD56.[15]

Primary cutaneous peripheral T-cell lymphoma, unspecified

The term primary cutaneous peripheral T-cell lymphoma, unspecified is used for CTCL that do not fit into one of the well-defined subtypes of CTCL described above. Within this broad category three provisional entities have been separated: aggressive epidermotropic $CD8^+$ CTCL, cutaneous gamma-delta T-cell lymphoma (CGD-TCL) and primary cutaneous $CD4^+$ small-medium pleomorphic T-cell lymphoma.[3] In general, these cutaneous PTL, unspecified have a poor prognosis. Distinction between primary and secondary cutaneous involvement is less important than in other types of cutaneous lymphoma. Patients presenting with only skin lesions generally develop extracutaneous disease within a short period of time and have a poor prognosis as well. The only exception is the group of primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphomas, which have a favorable prognosis (5-year survival >80%), in particular in cases presenting with a solitary or localized skin lesions.[16] The clinical characteristics and prognostic features of other PTL, unspecified are discussed in the previous chapter.

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