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Prognostic factors in cutaneous T-cell lymphoma

Introduction

Cutaneous T-cell lymphoma (CTCL) are a heterogeneous group of neoplasms of skin-homing T cells that show considerable variation in clinical presentation, histological appearance, immunophenotype and prognosis. In recent classification schemes (WHO-EORTC; WHO 2008) roughly three categories of CTCL can be distinguished: (1) the group of classical CTCL, including mycosis fungoides (MF, variants or subtypes of MF (folliculotropic MF; pagetoid reticulosis; granulomatous slack skin) and Sézary's syndrome (SS); (2) the group of primary cutaneous CD30-positive lymphoproliferative disorders ($CD30^+$ LPD); and (3) 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 (PTL, NOS) as well as some rare subtypes of PTL, NOS.[1,2]

Classification according to these new classification schemes 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 summarized and prognostic factors within these categories are discussed.

Mycosis fungoides

Mycosis fungoides (MF) represents the most common type of CTCL and accounts for approximately 65% of all CTCL.[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 above all dependent on the stage, and in particular the type and extent of skin lesions and the presence of extracutaneous disease.[3-5]. Patients with limited 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.[4] Apart from stage of disease, absence of complete remission after initial treatment, the presence of follicular mucinosis, and low numbers of $CD8^+$ T-cells in the dermal infiltrates or within the peripheral blood have been described to be independently associated with a reduced survival.[4,6,7] Subsequent studies defined folliculotropic MF as 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. The more unfavorable prognosis of folliculotropic MF as compared to classical MF has been explained by the deep (peri)follicular localization of the neoplastic infiltrates, making them less accessible to skin-targeted therapies.[8,9] Risk factors associated with an aggressive clinical course in MF include the presence of effaced lymph nodes, visceral involvement, and transformation into a large T-cell lymphoma, defined by the presence of more than 25% blast cells in the dermal infiltrate.[10]

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 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) or an absolute Sézary cell count of least 1000 cells per mm^3.[1]

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 is the most important prognostic parameter in SS.[11,12] In addition, advanced age (>65), a short period between the onset of skin lesions and diagnosis, high levels of LDH and β-2-microglobulin, lymph node stage and the presence of large circulating Sezary cells (>15 μm) have been reported as poor prognostic factors.[11-14] However, assessment of the clinical significance of these factors is seriously hampered by differences in diagnostic criteris for SS in these studies, and by the fact that most studies involved mixed populations of patients with MF and SS.

Primary cutaneous $CD30^+$ lymphoproliferative disorders

Primary cutaneous $CD30^+$ lymphoproliferative disorders represent the second most common group of CTCL, accounting for approximately 25% of CTCL.[1] 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 disease. Clinically, C-ALCL generally present with solitary or localized nodules or tumors that often develop ulceration, they may show partial or complete spontaneous regression, frequently relapse in the skin, but extracutaneous dissemination is uncommon and occurs in approximately 10% of the patients.[15] LyP is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a ($CD30^+$) 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 3-12 weeks. 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. Differentiation between both 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 have a $CD4^+$ T-cell phenotype with variable loss of CD2, CD5 and/or CD3, and express cytotoxic proteins (granzyme B, TIA-1, perforin) in approximately 70% of the cases. Unlike systemic ALCL, most C-ALCL 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%.[15,16] In previous studies it was suggested that patients presentating with extensive limb involvement or with lesions in the head and neck region have a reduced survival, while age below 60 years and spontaneous remission were associated with a more favorable prognosis.[16-18] In a recent study on 135 C-ALCL patients only extensive leg involvement, but none of the other parameters suggested previously, was found to be associated with a more aggressive clinical course.[19]

LyP also has an excellent prognosis. In a 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.[15] Risk factors for the development of systemic lymphoma are unknown.

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined as a cytotoxic alpha/beta T-cell lymphoma characterized by the presence of primarily subcutaneous infiltrates of small, medium-sized or large pleomorphic T-cells and many macrophages, typically with karyorrhexis of tumour cells and associated fat necrosis. In contrast to the third edition of the WHO classification (2001), in the WHO-EORTC classification and in the WHO 2008 classification, cases expressing the γ/δ T-cell receptor are excluded, and reclassified as primary cutaneous γ/δ T-cell lymphoma (PCGD-TCL).

SPTCL occur in adults as well as in young children. In a recent EORTC study including 63 SPTCL patients, the median age at presentation was 36 years, approximately 20% of patients was under the age of 20, and the female-to-male ratio was 2:1.[20] 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 may be

present in over 50% of patients. Laboratory abnormalities, including cytopenias and elevated liver function tests are common, and a frank hemophagocytic syndrome (HPS) is observed in approximately 15% of patients. Dissemination to extracutaneous sites is rare. Hepatosplenomegaly may be seen, but is generally not due to lymphomatous involvement.

Histopathology reveals subcutaneous infiltrates simulating a lobular panniculitis showing small, medium-sized or sometimes large pleomorphic T cells with hyperchromatic nuclei and often many macrophages. The overlying epidermis and dermis are typically uninvolved. Rimming of individual fat cells by neoplastic T cells is a helpful, though not completely specific diagnostic feature. Necrosis, karyorrhexis, cytophagocytosis and fat necrosis are common findings. The neoplastic T-cells have a mature α/β^+, $CD3^+$, $CD4^-$, $CD8^+$ T-cell phenotype, with expression of cytotoxic proteins. The neoplastic T-cells express beta F1 and are negative for CD56, facilitating differentiation from cutaneous gamma/delta T-cell lymphoma.[20-22] CD30 is rarely, if ever, expressed. EBV is abent.

Prognosis and predictive factors

SPTCL have a favorable prognosis with a 5-year overall survival (OS) of approximately 80%.[20,22] The presence of a HPS is the most important risk factor. In a recent EORTC study patients with and without an associated HPS had a 5-year OS of 46% and 91%, respectively.[20]

Primary cutaneous peripheral T-cell lymphoma, not otherwise specified

In the third edition of the WHO classification (2001) the term peripheral T-cell lymphomas, not otherwise specified (PTL, NOS) was used for all T-cell neoplasms that did not fit into one of the better defined subtypes of T-cell lymphoma/leukemia. These PTL, NOS represent a heterogeneous group and not uncommonly involve the skin, either as primary or secondary manifestation of the disease. Primary cutaneous PTL, NOS are rare and constitute less than 10% of all CTCL.[1] More recent studies have recognized some better defined subtypes within this heterogeneous group of neoplasms, which have subsequently been included as provisional entities in the WHO-EORTC classification. These include primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, and primary cutaneous $CD4^+$ small-medium pleomorphic T-cell lymphoma. In the WHO 2008 classification these three groups have been maintained as (provisional) entities and have been included in a separate chapter 'primary cutaneous peripheral T-cell lymphoma, rare subtypes'. For cases that do not fit into any of these three subgroups the designation primary cutaneous PTL, NOS is maintained. It should be emphasized that in all cases with a histologic diagnosis of PTL-NOS a diagnosis of MF must be ruled out by complete clinical examination and an accurate clinical history.

Primary cutaneous γ/δ T-cell lymphoma

Primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL) is a lymphoma composed of a clonal proliferation of mature, activated γ/δ T cells with a cytotoxic phenotype. This group includes cases previously known as SPTCL with a γ/δ phenotype.

PCGD-TCL generally present with disseminated plaques and/or ulceronecrotic nodules or tumors, particularly on the extremities, but other sites may be affected as well.[20,23] Involvement of mucosal and other extranodal sites is frequently observed, but involvement

of lymph nodes, spleen or bone marrow is uncommon. A HPS may occur in (ca. 50%) patients with panniculitis-like tumors.[20,23,24]

Three major histologic patterns of involvement can be present in the skin: epidermotropic, dermal and subcutaneous. Often more than one histologic pattern is present in the same patient in different biopsy specimens or within a single biopsy specimen.[20,23,24] The subcutaneous cases may show rimming of fat cells, similar to SPTCL of alpha/beta origin, but in addition usually show dermal and/or epidermal involvement. The neoplastic cells are generally medium to large in size with coarsely clumped chromatin. These cells characteristically have a $\beta F1^-$, $CD3^+$, $CD2^+$, $CD4^-$, $CD5^-$, $CD7^{+/-}$, $CD8^-$, $CD56^+$ phenotype with strong expression of cytotoxic proteins. Apoptosis and necrosis are common, often with angioinvasion. EBV is negative.

Prognosis and predictive factors

PCGD-TCL are resistant to multi-agent chemotherapy and have a poor prognosis with a median survival of approximately 15 months.[20,23] Patients with subcutaneous fat involvement tend to have a more unfavorable prognosis than patients with epidermal or dermal disease only.[23] In a recent study including 20 patients with panniculitis-like tumors the 5-year overall survival was 11%; no differences in survival were found between cases with or without HPS, neither between $CD56^+$ and $CD56^-$ cases.[20]

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

CTCL characterized by a proliferation of epidermotropic $CD8^-$ cytotoxic T-cells and an aggressive clinical behavior. Clinically, these lymphomas are characterized by the presence of localized or disseminated eruptive papules, nodules and tumors showing central ulceration and necrosis or by superficial, hyperkeratotic patches and plaques.[25] These lymphomas may disseminate to other visceral sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared.[25,26]

The histological appearance is very variable ranging from a lichenoid pattern with marked, pagetoid epidermotropism and subepidermal edema to deeper, more nodular infiltrates. The epidermis may be acanthotic or atrophic, often with necrosis, ulceration and variable spongiosis, sometimes with blister formation. Angiocentricity and angioinvasion may be present. Tumour cells are small-medium or medium-large with pleomorphic or blastic nuclei. They have a $\beta F1^+$, $CD3^+$, $CD8^+$, granzyme B^+, $perforin^+$, $TIA\text{-}1^+$, $CD45RA^{+/-}$, $CD45RO^-$, $CD2^{-/+}$, $CD4^-$, $CD5^-$, $CD7^{+/-}$ phenotype.[22,25-27] EBV is negative.

Prognosis and predictive factors

These lymphomas often have an aggressive clinical course with a reported median survival of 32 months.[25] In a recent EORTC study the prognosis was even worse. After a median follow-up of 13 months, 16 of 20 patients had died of lymphoma (Robson, A. *et al*; in preparation).

These aggressive $CD8^+$ cytotoxic CTCL should be distinguished from cases of classical MF with a $CD8^+$ T-cell phenotype, which have the same clinical behaviour and prognosis as $CD4^+$ MF cases, and from a recently defined entity designated indolent $CD8^+$ lymphoid proliferation of the ear.[28] 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. These lesions show a dense, diffuse and non-epidermotropic infiltrates of monomorphous medium-sized blast cells with

small nucleoli and clear chromatin. These cells have a CD3$^+$, CD4$^-$ CD8$^+$, TIA-1$^+$, granzyme B$^-$, CD30$^-$ T-cell phenotype and the proliferation rate is generally low. 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. Recognition that these patients have an indolent clinical behaviour, despite an aggressive histology, should prevent unnecessarily aggressive treatment.

Primary cutaneous CD4$^+$small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL)

CTCL defined by a predominance of small to medium-sized CD4$^+$ pleomorphic T-cells without (a history of) patches and plaques typical of MF and in most cases a favorable clinical course.[29]

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.[29-31]

Histologically, these lymphomas show dense, diffuse or nodular infiltrates within the dermis with tendency to infiltrate the subcutis. Epidermotropism may be present focally. There is a predominance of small/medium-sized pleomorphic T cells with a CD3$^+$, CD4$^+$, CD8$^-$, CD30$^-$ phenotype. The proliferation rate is generally low. Cytotoxic proteins are not expressed. A small proportion (<30%) of large pleomorphic cells may be present.[29] In most cases a considerable admixture with reactive CD8$^+$ T-cells, B-cells, plasma cells and histiocytes may be observed, making distinction from a reactive process (pseudo-T cell lymphoma) difficult in some cases.[31] Demonstration of an aberrant T-cell phenotype and clonality are useful criteria suggesting a diagnosis of PCSM-TCL.[32]

Prognosis and predictive factors

These lymphomas have a rather favorable prognosis with an estimated 5-year survival of approximately 80%.[29-31] Particularly, cases presenting with a solitary or localized skin lesions 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.[30] Recognition of this entity, separate from other primary cutaneous PTL, NOS is important to avoid unnecessarily aggressive treatment of these patients.

(Primary cutaneous) peripheral T-cell lymphoma, not otherwise specified

The designation (primary cutaneous) PTL-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. Differentiation between primary and secondary cutaneous involvement seems less important than for other types of malignant lymphoma involving the skin.[29]

Patients are commonly adults, who present with solitary or localized, but more frequently generalized nodules or tumors.[29,33,34] Histologically, these lymphomas show nodular or diffuse infiltrates with variable numbers of medium-sized to large pleomorphic or immunoblast-like T-cells. Large neoplastic cells represent at least 30% of the total tumor cell population. Most cases show an aberrant CD4$^+$ T-cell phenotype with variable loss of pan-T cell antigens. CD30 staining is negative or restricted to few scattered tumor cells. Rare cases may show co-expression of CD56. Expression of cytotoxic proteins is uncommon in CD4$^+$ cases, but frequently observed in cases with a CD4$^-$, CD8$^-$ T-cell phenotype.[29] The prognosis is generally poor with 5-year survival rates of less than 20%.[29,33,34] No difference

in survival is found between cases presenting with solitary or localized lesions and cases presenting with generalized skin lesions.[29]

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