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Cutaneous T-cell lymphomas: histology

M. SANTUCCI

Department of Human Pathology and Oncology University of Florence Medical School, Florence, Italy

Non-Hodgkin's lymphomas are a heterogeneous group of tumors that arise from the lymphoreticular system. Approximately one third of non-Hodgkin's lymphomas occur in extranodal sites, and the skin is the second most common site of extranodal involvement after the gastrointestinal tract.

Primary cutaneous lymphomas often have a different clinical behaviour and prognosis from histologically similar systemic lymphomas involving the skin secondarily, and therefore require different types of therapies. For that reason, recent classification systems such as the EORTC classification for primary cutaneous lymphomas[1] and the WHO classification for tumours of haematopoietic and lymphoid tissues[2] considered primary cutaneous lymphomas as separate entities. Although there was consensus between the EORTC and WHO schemes on the classification of most types of primary cutaneous T-cell lymphomas (CTCLs), remaining differences between the two classification systems resulted in considerable debate and confusion. During two consensus meetings held in Lyon, France (September 2003) and in Zurich, Switzerland (January 2004), these differences were resolved by a group of pathologists and dermatologists representatives of both classification schemes, and a consensus classification was developed: the WHO-EORTC classification for primary cutaneous lymphomas.[3-6] The new WHO-EORTC classification has been developed on the base of the EORTC classification for cutaneous lymphomas1 and the WHO classification for nodal lymphomas.[2] This report will focus on primary cutaneous T-cell and NK-cell lymphomas.

Mycosis fungoides

Mycosis fungoides (MF) is the prototype of primary CTCLs; the disease presents in the skin and shows a characteristic stepwise clinical progression with potential extracutaneous involvement. MF starts with patches, which after years/decades evolve into plaques; in a minority of cases, the disease develops tumours and extracutaneous spread (lymph nodes, blood, bone marrow, internal organs).

The histological diagnosis of MF in its early stages is difficult to establish, as the disease may closely resemble dermatitis.[7,8] Early patch lesions show a superficial band-like (lichenoid) infiltrate, mainly composed of lymphocytes and histiocytes; eosinophils or plasma cells are absent. Atypical lymphocytes with medium- to large-sized (7-9 μm in diameter), extremely convoluted (cerebriform), and sometimes hyperchromatic nuclei (so-called medium-large cerebriform cells, which are the diagnostic cells) are few, and mostly confined to the epidermis (epidermotropism).[9] They characteristically colonize the basal layer of the epidermis either as single, often haloed cells, or in linear configuration.

In plaques, the histological findings are most often fully diagnostic. The epidermotropism is more pronounced and the presence of intraepidermal collections of atypical cells (Pautrier microabscesses) is a highly characteristic feature, although observed in only a minority of cases.[8] There may be mild acanthosis, hyperkeratosis, oedema or fibrosis of the papillary dermis. The infiltrate may contain an admixture of eosinophils, plasma cells, macrophages, reactive lymphocytes, and dendritic cells.[10] With progression to tumour stage, the dermal infiltrate becomes diffuse and epidermotropism is frequently lost. The tumour cells increase both in number and size, and may include cells with small, medium-sized, and large cerebriform nuclei, and blast cells with large nuclei and prominent nucleoli. There is a decrease in the

numbers of reactive T-cells and dendritic cells. Eosinophils and plasma cells usually are present.[10] Tumour cells have a mature $CD3^+$, $CD4^+$, $CD45RO^+$ memory T-cell phenotype. In rare cases, a $CD4^-/CD8^+$ mature T-cell phenotype may be documented (MF, cytotoxic immunophenotype variant). Such cases have the same clinical behaviour and prognosis as $CD4^+$ cases. During progression of the disease loss of CD2, CD5, and CD7 may be observed. When large blast stage occurs, cells can express the CD30 molecule and/or a cytotoxic phenotype.

MF variants and subtypes

Apart from the classical Alibert-Bazin type of MF, many clinical and/or histological variants have been described. Clinical variants-such as acanthosis nigricans-like, bullous/dyshidrotic, hypo- or hyperpigmented, hyperkeratotic, ichtyosis-like, perioral dermatitis-like, pigmented purpura-like, poikylodermatous, verrucous, zosteriform MF-have a clinical behaviour similar to that of classical MF, and therefore are not considered separately in the new WHO-EORTC classification. In contrast, folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin have sufficient distinctive clinicopathologic features to deserve separate consideration.

Folliculotropic MF

Folliculotropic MF is a variant of MF characterized by the presence of folliculotropic infiltrates and preferential involvement of the head & neck area. The most characteristic finding is the deep (perivascular and periadnexal) localization of the neoplastic infiltrate-which makes tumour cells less accessible to skin-targeted therapies-with infiltration of the follicular epithelium by cerebriform lymphocytes, and sparing of the epidermis (folliculotropism instead of epidermotropism). Many cases show follicular mucinosis (mucinous degeneration of the follicular epithelium). There is often a considerable admixture of eosinophils and plasma cells. In most cases, neoplastic T-cells have a $CD3^+$, $CD4^+$ phenotype as in classical MF.

Pagetoid reticulosis

Pagetoid reticulosis is a variant of MF characterized by the presence of localized, slowly progressive patches or plaques, usually located on the limbs, with an intraepidermal proliferation of atypical T-lymphocytes, singly or arranged in nests (pagetoid picture). The atypical cells have medium- to large-sized nuclei and abundant cytoplasm. The dermis generally does not contain tumour cells. Immunophenotypically, tumour cells may be either $CD4^+/CD8^-$ or $CD4^-/CD8^+$; CD30 is often expressed. The term pagetoid reticulosis should only be used for the localized type (Woringer-Kolopp type) and not for the disseminated type (Ketron-Goodman type). Disseminated cases would currently be classified as primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma, cutaneous γ/δ T-cell lymphoma, or tumour-stage MF.

Granulomatous slack skin

Granulomatous slack skin is an extremely rare subtype of CTCL characterized by the slow development of pendulous folds of lax skin in the major skin folds (axillae and groins) and histologically by a granulomatous infiltrate with clonal T-lymphocytes. In approximately one-third of the reported patients, an association with Hodgkin's lymphoma or classical MF has been reported. The disease has an indolent clinical course. Histologically, fully developed lesions show a dense granulomatous dermal infiltrate composed of cerebriform T-lymphocytes, macrophages, and variable numbers of multinucleated giant cells; destruction of elastic tissue is commonly observed. The atypical T-lymphocytes have a $CD3^+$, $CD4^+$ phenotype.

Sézary syndrome

Sézary syndrome (SS) is a rare disease historically defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells (Sézary cells) in skin, lymph nodes, and peripheral blood. Recently, the International Society for Cutaneous Lymphomas,[11] has recommended as criteria for the diagnosis of SS one or more of the following: (i) an absolute Sézary cell count of at least 1000 cells/mm^3; (ii) demonstration of immunophenotypical abnormalities (an expanded $CD4^+$ T-cell population resulting in a CD4/CD8 ratio > 10; loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5; or both); or (iii) the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods. The histological picture is similar to that of MF. However, the cellular infiltrate in SS is generally more monotonous and epidermotropism may be absent. Immunophenotypically, tumour cells most often have a $CD3^+$, $CD4^+$ phenotype.

Primary cutaneous CD30+ lymphoproliferative disorders

Primary cutaneous CD30+ lymphoproliferative disorders are the second most common category of CTCLs, accounting for approximately 30% of CTCLs. This group includes primary cutaneous anaplastic large cell lymphoma (C-ALCL) and lymphomatoid papulosis (LyP). C-ALCL and LyP

form a spectrum of disease, and histological criteria alone are quite often not sufficient to differentiate between them. The clinical appearance and course are used as decisive criteria for the definite diagnosis and choice of therapy.[12]

Primary cutaneous anaplastic large cell lymphoma

C-ALCL is composed of large cells with an anaplastic, pleomorphic, or immunoblastic morphology and expression of the CD30 antigen by the majority (> 75%) of tumour cells. There is no clinical evidence or history of LyP, MF, or another type of CTCL. Most patients present with solitary or localized nodules or tumours, often showing ulceration. Diffuse lesions are observed in approximately 20% of cases. Lesions may show spontaneous regression as in LyP. C-ALC frequently relapses. Extracutaneous dissemination may occur in about 10% of cases (mainly regional lymph nodes). Histologically, there is a diffuse, non-epidermotropic infiltrate with cohesive sheets of large CD30+ tumour cells. Most frequently, tumour cells have the appearance of anaplastic cells (with round, oval, or irregularly shaped nuclei, prominent eosinophilic nucleoli, and abundant cytoplasm), less commonly (approximately 20%-25% of cases), they have a pleomorphic or immunoblastic cytomorphology. Ulcerating lesions may show a LyP-like histological picture, with an abundant inflammatory infiltrate composed of reactive T-lymphocytes, histiocytes, eosinophils and/or neutrophils, and relatively few CD30+ tumour cells. Neoplastic cells generally show an activated CD4+ T-cell phenotype with variable loss of CD2, CD3, and CD5, and frequent expression of cytotoxic molecules (TIA-1, granzyme B, perforin). CD30 antigen must be expressed by the majority (> 75%) of the neoplastic T-lymphocytes. Unlike systemic CD30+ lymphomas, most C-ALCs express the cutaneous lymphocyte antigen (CLA), but do not express the epithelial membrane antigen (EMA) and the anaplastic lymphoma kinase (ALK; indicative of the t2;5 chromosomal translocation or its variants).

Lymphomatoid papulosis

LyP is historically defined as *a self-healing, rhythmic, paradoxic eruption histologically malignant but clinically benign.* LyP generally occurs in adults but may occur in children as well. LyP is characterized by the presence of papular, papulonecrotic, and/or nodular skin lesions at different stages of development, predominantly located on the trunk and limbs. Individual skin lesions disappear within approximately 3-12 weeks, and may result in superficial scars. In about 20% of patients, LyP may be preceded by, associated with, or followed by another type of lymphoma (MF, C-ALCL, Hodgkin's lymphoma).

The histological picture of LyP is extremely variable. Three histological subtypes have been described. In LyP type A, scattered or small clusters of large, multinucleated or Reed-Sternberg-like, CD30+ lymphocytes are intermingled with numerous inflammatory cells (reactive lymphocytes, histiocytes, neutrophils, and/or eosinophils). LyP type B is very rare and is characterized by an epidermotropic infiltrate of small cerebriform lymphocytes (the histological picture has some resemblance with that observed in MF). LyP type C shows large clusters of large CD30+ T-lymphocytes with relatively few admixed inflammatory cells. The large atypical lymphocytes in LyP type A and C have the same phenotype as tumour cells in C-ALCL. The cerebriform lymphocytes of LyP type B do not express the CD30 molecule.

Subcutaneous panniculitis-like T-cell lymphoma

Recent studies have suggested that two groups of subcutaneous panniculitis-like T-cell lymphoma (SPTL) with different histology, phenotype, and clinical course can be identified.[13] SPTLs with an α/β T-cell phenotype are usually CD8+, are confined to the subcutaneous tissue (no dermal and/or epidermal involvement), and generally run an indolent clinical course. In contrast, SPTLs with a γ/δ T-cell phenotype (roughly 25% of all cases) are typically $CD4^-/CD8^-$, often express CD56, the neoplastic infiltrate is not limited to the subcutaneous tissue (frequent dermal and/or epidermal involvement), and have a very aggressive course. In the WHO-EORTC classification the term SPTL is only used for cases with an alpha/beta T-cell phenotype. Cases with a gamma/delta T-cell phenotype are included in the category of cutaneous γ/δ T-cell lymphomas. Patients generally present with solitary or multiple nodules and/or plaques, which mainly involve the lower limbs. Systemic symptoms (fever, fatigue, weight loss) may be present. Association with a haemophagocytic syndrome (generally indicative of an aggressive course) is definitely less frequent than in cutaneous γ/δ T-cell lymphomas with a panniculitis-like histological picture. Extracutaneous dissemination is rare. SPTL may be preceded for years/decades by a seemingly benign panniculitis. Histologically, there is a subcutaneous infiltrate composed of small, medium-sized, or large pleomorphic T-lymphocytes, often admixed with numerous macrophages; the picture may resemble a benign panniculitis. The overlying epidermis and dermis are typically uninvolved. Rimming of individual adipocytes by tumour cells is a

helpful, although not specific, diagnostic feature. Necrosis, karyorrhexis, and cytophagocytosis are common findings. In the early stages of the disease, the neoplastic infiltrate may lack significant atypia and a heavy inflammatory infiltrate may predominate. Immunophenotypically, SPTL shows an α/β^+, $CD3^+$, $CD8^+$ T-cell phenotype, with a strong expression of cytotoxic molecules (TIA-1, granzyme B, perforin).

Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type, is an EBV+ lymphoma composed of small, medium, or large cells usually with an 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. Patients generally present with multiple plaques/tumours preferentially located on the trunk and limbs. Ulceration is quite common. Systemic symptoms (fever, malaise, weight loss) may be present; a few cases may be accompanied by a haemophagocytic syndrome. The histological picture is characterised by a dense infiltrate involving the dermis and the subcutis, often with an evident epidermotropism. Angiocentric and angiodestructive phenomena are almost always extensive and characteristically accompanied by prominent necrosis. NK/T-cell lymphoma shows a broad cytomorphological spectrum ranging from small to large lymphocytes, with most cases consisting of medium-sized cells. Tumour cells have irregular or oval nuclei, moderately dense chromatin, and pale cytoplasm. A heavy inflammatory infiltrate can be seen. Tumour cells are $CD2^+$, $CD56^+$, cytoplasmic $CD3\varepsilon^+$ (surface CD3 is negative), strongly express cytotoxic molecules (TIA-1, granzyme B, perforin), and are EBV^+ by *in situ* hybridization.

Primary cutaneous peripheral T-cell lymphoma, unspecified

The category peripheral T-cell lymphoma (PTL), unspecified, represents a sort of wastebasket which encompasses all T-cell malignancies that do not fit into any of the defined subtypes of CTCL (less than 10% of all CTCLs).

They are $CD30^-$ and most frequently show an aggressive clinical behaviour. Recent studies have supported the hypothesis that primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma, cutaneous γ/δ T-cell lymphoma, and primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma can be separated out as provisional entities. For the remaining cases that do not fit into any of these provisional entities the designation PTL, unspecified, is used.

Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma (provisional entity). Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma is a lymphoproliferative disorder characterized by a proliferation of $CD8^+$ cytotoxic T-cells with a strong epidermotropism and a very aggressive clinical course. Patients present either with localized/disseminated eruptive papules, nodules, and tumours with central ulceration and necrosis or with superficial, hyperkeratotic patches and plaques.

The clinical picture shares similarities with cutaneous γ/δ T-cell lymphoma and cases described in the past as generalized pagetoid reticulosis (Ketron-Goodman type).

Differentiation from other types of CTCL expressing a $CD8^+$ cytotoxic T-cell phenotype (pagetoid reticulosis, MF, LyP, C-ALCL) may require taking into account the clinical presentation and behaviour. Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma may disseminate to visceral sites (lung, testis, central nervous system, oral mucosa), while lymph nodes are generally spared. Histologically, there is a pagetoid pattern with a striking epidermotropism showing acanthosis, spongiosis (sometimes with blister formation), necrosis, and ulceration. Angiocentricity and angioinvasion may be present. Neoplastic lymphocytes are small-medium or medium-large in size with pleomorphic or blastic nuclei. Tumour cells show an α/β^+, $CD3^+$, $CD8^+$, $CD45RA^+$ phenotype, with a strong expression of cytotoxic molecules (TIA-1, granzyme B, perforin).

Cutaneous γ/δ T-cell lymphoma (provisional entity)

Cutaneous γ/δ T-cell lymphoma is a lymphoproliferative disorder characterized by a clonal proliferation of mature, activated γ/δ T-lymphocytes with a cytotoxic phenotype. This subtype includes cases previously known as SPTL with a γ/δ T-cell phenotype. Patients generally present with ulceronecrotic plaques, nodules, and/or tumours disseminated particularly on the limbs. Involvement of extranodal sites is frequently observed; involvement of lymph nodes, spleen, or bone marrow is uncommon. A haemophagocytic syndrome may occur in patients with a panniculitis-like histological picture. Three histological patterns of involvement can be observed: epidermotropic, dermal, and subcutaneous. Quite often more than one histological pattern is present in the same patient either in different biopsy specimens or within a single biopsy specimen. More often, tumour cells

are medium to large in size with coarsely clumped chromatin; large blastic cells with vesicular nuclei and prominent nucleoli are rare. Apoptosis, necrosis, and angioinvasion are frequently observed. Tumour cells typically have a γ/δ^+, $CD2^+$, $CD3^+$, $CD56^+$ phenotype with a strong expression of cytotoxic molecules (TIA-1, granzyme B, perforin); most cases are $CD4^-/CD8^-$, although CD8 may be expressed in a few cases.

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

Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma is a CTCL defined by a predominance of small- to medium-sized $CD4^+$ pleomorphic T-cells without (a history of) patches and plaques typical of MF; in most cases, the disease has a favourable clinical course. Similar cases with a $CD8^+$ cytotoxic T-cell phenotype have an aggressive clinical course and are included in the group of primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphomas. More frequently, patients present with a solitary plaque/tumour, generally on the face, the neck, or the upper trunk; less commonly, they present with several papules, nodules, or tumours. Histologically, these lymphomas show nodular or dense, diffuse infiltrates involving the dermis and sometimes the subcutis. Epidermotropism may be present, but is never prominent. Small/medium-sized pleomorphic T-cells predominate. A proportion (<30%) of large pleomorphic cells may be present. Often a considerable admixture with reactive lymphocytes and histiocytes may be seen. Tumour cells have a $CD3^+$, $CD4^+$ phenotype; cytotoxic proteins are not expressed.

Primary cutaneous peripheral T-cell lymphoma, unspecified

The designation PTL, unspecified, is maintained for lymphoproliferative disorders that do not fit either into any of the well defined subtypes of CTCL or the three aforementioned provisional entities. Patients present with solitary, localized, or more frequently generalized nodules and/or tumours. Histologically, lesions show a nodular or diffuse infiltrate composed of medium- to large-sized pleomorphic or immunoblast-like T-cells. Large tumour cells are more than 30% of the total neoplastic cell population. Epidermotropism is mild or absent. Most frequently, neoplastic cells show a $CD4^+$ T-cell phenotype, with variable loss of pan-T-cell antigens. CD30 is negative or expressed by few scattered neoplastic cells. Occasionally, there can be co-expression of CD56 antigen and cytotoxic molecules.

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