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CUTANEOUS LYMPHOMA: A CLINICALLY RELEVANT CLASSIFICATION

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Should there be a new, "original" classification of lymphoproliferative diseases affecting the skin? Please, no. In this review, we stress the current concept of cutaneous lymphoma (CL) and propose a simplified classification with therapeutic and prognostic relevance, basing it upon both classic and recently defined or clearly redefined clinicopathologic entities. For this reason, we adhere as strictly as possible to clinical facts and to clinicopathologic-immunologic correlations. Indeed, the development of the present concept of CL has been largely influenced by the continuously increasing amount of available data concerning its immunophenotypic and genotypic features and their correlation with clinical and histologic patterns.

PREREQUISITES

The first prerequisite for the classification of CL is its definition. It should be now accepted that the involvement of the skin secondary to nodal lymphomas is something completely different from CL. This latter term should only concern lymphomas which present in the skin, in the absence of any detectable extracutaneous lesion—despite careful and complete staging procedures—for at least 6 months from diagnosis. The diagnosis of CL and its differentiation from reactive lymphoproliferative disorders (pseudolymphomas) are now supported by immunophenotyping and genotyping. The demonstration of clonality is now accepted by most people as the key criterion for the diagnosis of CL and its differentiation from pseudolymphoma. This latter term has been widely used among dermatologists and dermatopathologists to indicate lymphoproliferative cutaneous disorders characterized by histologic features suggestive of malignancy, by an indolent clinical

course, and a good response to nonaggressive treatment. It is now clear that lymphomas (i.e., monoclonal proliferations of lymphoid cells) primarily presenting in the skin often have a favorable prognosis; the same holds true for other organ-related lymphomas, e.g., the so-called MALT lymphoma (lymphoma of the mucosa-associated lymphoid tissue).¹ Therefore, the immunohistochemical finding of immunoglobulin (Ig) light chain monoclonal restriction by neoplastic B-cells and/or the demonstration by DNA analysis of a monoclonal rearrangement of Ig heavy chain or T-cell receptor genes should be considered the most reliable criteria for the diagnosis of lymphoma,^{2,3} especially when the histologic features are not conclusive. The term pseudolymphoma, consequently, should be restricted to skin lesions histologically mimicking lymphoma but characterized by polyclonal proliferations of T- or B-cells and/or clearly related to environmental stimuli: insect or arthropod bites, tattoos, infections with *Borrelia burgdorferi*, drugs (anticonvulsants, angiotensin-converting enzyme inhibitors), chemicals (lymphomatoid contact dermatitis), or associated with extreme light hypersensitivity (actinic reticuloid).

TWO MAIN GROUPS

According to histoimmunologic (and genotypic) features, CL can be divided into two main groups: cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL). This distinction reflects some basic clinical and biologic differences. In fact, the long-term behaviour and prognosis of CTCL are, as a rule, more aggressive and less favorable than those of CBCL. Furthermore, the treatment of CTCL may be a great problem in terms of either rate of complete remission or possibility to maintain a sustained complete remission. As shown later in this review, another important difference concerns the prognostic relevance of the type and extent of skin lesions; this is high (with few but important exceptions) in CTCL, while it is definitely lower in CBCL.

CUTANEOUS T-CELL LYMPHOMA

Cutaneous T-cell lymphoma is a term introduced by Edelson almost twenty years ago⁴ to indicate a group

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of lymphoproliferative diseases of the skin, including classic mycosis fungoides (MF), Sézary syndrome (SS), and some related disorders. The general features of CTCL, according to Edelson's proposal,⁵ were: (1) exclusive or predominant involvement of the skin; (2) degree of epidermotropism directly related to the apparent level of neoplastic cell maturity (i.e., CD4+ helper phenotype and "cerebriform" morphology); (3) natural progression from localized to disseminated cutaneous disease; and (4) evolution from slowly (cerebriform) to rapidly proliferating (blast) cell populations, the latter linked to a nonepidermotropic pattern of infiltration and poor prognosis. Consequently, the prognostically relevant staging system created for classic MF⁶ has been extended to CTCL in general. This type of nomenclature has the clear advantage to indicate reproducible criteria and to avoid the misleading use of eponyms. Some limitations cannot be ignored. The enormous amount of data derived from the clinicopathologic and biologic studies of the last ten years in this field clearly indicate that CTCL is indeed a heterogeneous group, in which different clinicopathologic categories can be identified. In fact, the natural history and prognosis of CTCL show a considerable degree of variations according to the clinicopathologic and immunophenotypic features of the disease at presentation. On this basis, we should like to distinguish at least three main subgroups: (1) mycosis fungoides; (2) CD30- CTCL (i.e., CD30 negative CTCL) non-MF; and (3) CD30+ CTCL non-MF. As discussed later in this paper, the prognostic relevance of other immunophenotypic and/or genotypic features, with the subsequent delineation of further clinicopathologic subgroups, needs to be evaluated on larger series of patients.

Mycosis fungoides is the "classic" CTCL, defined by its typical clinical course.⁷ This latter consists of an early, possibly very prolonged patch stage, a plaque stage, and a tumor stage. The *patch stage* is characterized by the presence of epidermal infiltration by medium-to-large cerebriform mononuclear cells (CMC), predominantly as single cells, and/or of discrete collections of medium-to-large CMC in the papillary dermis. According to the results of a recent study performed under the aegis of the European Organization for Research and Treatment of Cancer (EORTC)—Cutaneous Lymphoma Project Group (coordinator—Professor G. Burg, Zürich, Switzerland), the above-specified histologic features have to be considered as the most reliable criteria for the diagnosis of MF.⁸ The *plaque stage* is characterized by the typical band-like infiltration of CMC. The *tumor stage* is characterized by a diffuse infiltration of large blast cells and is associated with a rapidly fatal outcome. In the opinion of the members of the EORTC—Cutaneous Lymphoma Project Group, the diagnosis of MF is mainly supported by its typical clinical course. Indeed, the use of the term "MF à tumeur d'emée" (i.e., CL with the clinicopathologic features of tumor-stage MF,

but not preceded by the patch- and plaque-stages) is no longer acceptable. In fact, CTCL characterized by skin infiltration with large neoplastic cells at presentation is not necessarily associated with a poor prognosis,^{9,10} as discussed later. On the contrary, the occurrence of "blastic transformation" in tumor stage MF is always associated with a poor prognosis,¹¹ irrespective of the morphologic type of large T-cells according to the updated Kiel classification¹² (i.e., pleomorphic, large anaplastic, immunoblastic, or unclassifiable).

In the category of "CTCL non-MF," two main subgroups can be recognized according to the prevalent expression of the CD30 antigen—a peculiar activation marker—by neoplastic T-cells, irrespective of their morphology (pleomorphic, large anaplastic, immunoblastic, unclassifiable). CD30-CTCL non-MF are characterized by presentation with single, or more frequently, multiple skin nodules, plaques (Fig. 1) or tumors. Most of them are characterized clinically by a rapid course and poor prognosis despite aggressive treatment and histologically by a prevalently large cell morphology⁹ (primary cutaneous CD30- large cell lymphoma). A small proportion of CD30- CTCL non-MF may have a more prolonged course or a better prognosis. Some of these patients present with skin lesions clinically resembling plaque-stage MF (Fig. 2), but not preceded by a prolonged patch stage. Other patients present with isolated nodular lesions, which show a sustained complete remission after local orthovolt radiotherapy. Histologically, they are mostly, but not exclusively, characterized by a skin infiltration of small-to-medium sized pleomorphic T-cells.¹²

CD30+ CTCL non-MF are mostly characterized clinically by several signs as follow: presentation with solitary or localized skin lesions (Fig. 3); possible spontaneous regression (partial to complete); good and rapid response to local radiotherapy (orthovolt or megavolt); and favorable prognosis, despite frequent cutaneous re-



Figure 1. CD30- CTCL non-MF. Multiple, erythematous plaques, histologically characterized by a monotonous infiltration of large blastic cells (immunoblastic type), at presentation. The patient died of lymphoma 14 months after the diagnosis.



Figure 2. CD30- CTCL non-MF. Erythematous and scaling plaques on the back of a male patient. These lesions clinically resemble plaque-stage MF lesions, but are present for less than 2 months and have *not* been preceded by a prolonged patch stage. Histologically, they are characterized by a prevalent infiltration of small-to-medium sized, pleomorphic cells.

lapses. Histologically, they are characterized by skin infiltration of large T-cells, 75% or more of which express CD30 antigen irrespective of their morphologic classification, i.e., large anaplastic (anaplastic large cell, ALC) or not, according to the definition of the updated Kiel classification.¹² These cases are currently classified

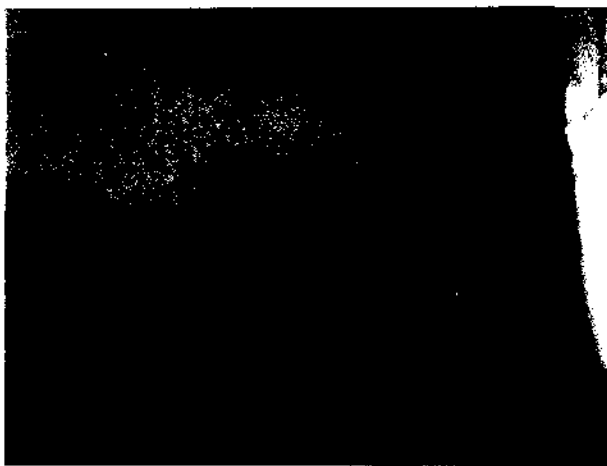


Figure 3. CD30+ CTCL non-MF. Primary cutaneous CD30+ large cell lymphoma: localized plaque, resulting from the growth and coalescence of small nodules. Histologically, this lesion showed a monotonous infiltration of CD30+ anaplastic large cells.

as primary cutaneous CD30+ large cell lymphomas^{9,10} and are considered by most experts as part of a spectrum of cutaneous lymphoproliferative disorders, all characterized by the presence of variable numbers of large CD30+ atypical cells (possibly of CD4+ T-helper activated origin), spontaneous regression of skin lesions, and benign course.¹³ This spectrum also includes two peculiar clinical entities: *regressing atypical histiocytosis*¹⁴ and *lymphomatoid papulosis*.¹⁵ These latter two conditions have been recently interpreted as T-cell disorders and proposed as CTCL on the basis of genotypic studies.¹⁶⁻¹⁸ Regressing atypical histiocytosis (RAH), originally considered a skin disease of histiocytic origin,¹⁴ is characterized by localized, slowly enlarging plaques, with an advancing, infiltrated border and an ulcerated central part; the lesions usually end in pigmentation and scarring (Fig. 4). Lymphomatoid papulosis (LYP), classically defined as "a continuing, self-healing eruption, clinically benign, histologically malignant,"¹⁵ is characterized by a typical pattern of skin lesions (Fig. 5): eruption of papulo-nodular lesions, ulceration, crusting, and self-healing without scarring. On the basis of the above data (presence of large CD30+ atypical cells, possible spontaneous regression of skin lesions, and benign course), it is reasonable to propose the classification of primary cutaneous CD30+ large cell (ALC and non-ALC) lymphomas, LYP, and RAH in the group of CD30+ CTCL non-MF.



Figure 4. CD30+ CTCL non-MF. Regressing atypical histiocytosis: large plaque of the upper part of the right thigh, surrounded by "satellite" papules, and showing the signs of its natural history: advancing infiltrated border, ulceration, pigmentation, and scarring.



Figure 5. CD30+ CTCL non-MF. Lymphomatoid papulosis: "a continuing, self-healing eruption, clinically benign, histologically malignant." Small, ulcerated plaque of the right upper eyelid. The evolution of skin lesions is typical: eruption of papulo-nodular lesions, ulceration, crusting, and self-healing without scarring.

The CD30 antigen expression by proliferating T-cells in the skin may have an important biologic implication. The same, however, may not be the case with other immunophenotypic and/or genotypic features of infiltrating T-cells. For example, a CD8+, CD4- phenotype of T-cells in CTCL has been associated with a poor prognosis,¹⁹⁻²² while others reported a different prognosis according to the loss or maintainance of certain other antigens: a more aggressive clinical course in the CD2-, CD7+ group; more indolent in the CD2+, CD7- group.²³ The so-called *gamma/delta* CTCL (i.e., proliferation of T-cells showing a monoclonal rearrangement of T-cell antigen receptor (TCR) gamma/delta chain genes) cannot be proposed as an entity with clinical and prognostic relevance at the moment. In fact, different features have been reported. On one hand, cases with aggressive behavior, showing different clinical features at presentation (disseminated, psoriasiform and crusted lesions,²⁴ tumors,²⁵ or multiple erythematous plaques).²⁵ On the other hand, cases with predominantly subcutaneous infiltration of gamma interferon producing, gamma/delta TCR+ cells, clinically present as a panniculitis and show a slowly progressive, indolent behavior.²⁶ In this latter case, interestingly, the neoplastic cells expressed CD30 antigen.

CUTANEOUS B-CELL LYMPHOMA

Cutaneous B-cell lymphoma (CBCL) has, according to data reported in the more detailed and consistent papers,²⁷⁻³⁰ a quite homogenous clinical behaviour. Most patients present with nodules and/or tumors, more often typically surrounded by small, slightly infiltrated

plaques and/or figurate erythematous lesions (Figs. 6, 7); the latter may have preceded for months to years the development of rapidly growing skin tumors. Skin lesions usually extend locally or regionally, widespread lesions at presentation being rare.³⁰ Orthovolt radiotherapy is highly effective and subjectively well-accepted and has to be considered the treatment of choice, either at presentation or on relapse. Chemotherapy is indicated in only a minority of patients (i.e., those with widespread cutaneous lesions and those who develop extracutaneous spread of the disease). The response to the above treatments is definitely good, with a high rate of complete remission.³⁰ In selected cases, surgical excision of isolated nodular lesions may be sufficient. Despite relatively frequent cutaneous relapses, CBCL show a low tendency to extracutaneous spread and a very low mortality rate.³⁰ According to our experience, no correlation exists between clinical features at presentation (type of lesions, single vs. multiple or localized vs. widespread lesions) and overall prognosis (extracutaneous spread and/or death of the patient). As in CTCL, the presence of skin lesions only should be referred to as stage I.³¹ Differing from CTCL, however, the identification of further clinical subgroups does not seem to have any prognostic relevance in CBCL.

Recent studies suggest the division of CBCL into two main groups: (1) those mainly composed of follicular center cell (FCC)-like large cells (defined as primary cutaneous large cell lymphomas of FCC origin²⁷); and (2)

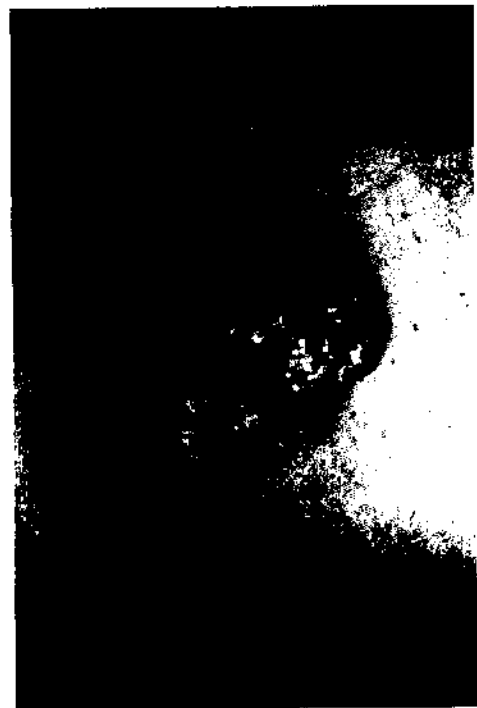


Figure 6. CBCL. Typical features at presentation: large tumorous lesion, with mamillated and shiny surface, on the back of a male patient. Slightly infiltrated plaques had preceded the rapid growth of the tumor for more than 6 years.



Figure 7. CBCL. Peculiar figured plaque of the anterior chest, resulting from the coalescence and growth of smaller, slightly infiltrated plaques.

those mainly composed of cells of plasmacytic origin, showing a monoclonal restriction of intracytoplasmic Ig (defined as primary cutaneous immunocytomas³²). This histologic distinction is paralleled on clinical grounds by different preferential sites of cutaneous presentation (trunk, head and neck in group 1, and lower limbs in group 2). Another recognized histologic subgroup is that of immunoblastic CBCL, mostly characterized by widespread, nodular lesions.^{31,33} In our experience, conversely, such correlations between clinical and pathologic features are not reproducible. In fact, a different morphologic diagnosis according to the updated Kiel classification¹² can be made on different lesions of the same patient, and even in different portions of the same lesion. In our experience, the histologic pattern in CBCL is largely related to the age and growth rates of skin lesions.³⁰ This ranges from the sometimes inconspicuous, "top heavy" infiltrate of intermediate-sized neoplastic B-cells and many reactive T-cells observed in early lesions ("low grade" malignancy picture, classically considered typical of cutaneous pseudolymphomas) to the uniformly heavy dermal infiltrate of large neoplastic B-cells ("high grade" malignancy picture) characteristic of late, rapidly growing lesions. Indeed, the histologic picture has no correlation with either the clinical course or the prognosis of CBCL, which is generally good. Therefore, at present, the identification of histomorphologic subgroups has no clinical, therapeutic, and/or prognostic relevance. The homogeneous clinical behavior, along with the uniform immunophenotypic (Leu8+, CD5-, CD10-)^{30,34,35} and genotypic features of neoplastic B-cells (lack of *bcl-2* gene rearrangement),^{28,34} strongly support the single nature of CBCL.³⁰ The striking similarities between CBCL^{30,35} and MALT lymphoma¹ (preferentially locoregional extension, nonaggressive clinical behavior, good response to local treatment, histologic

finding of so-called centrocyte-like cells in all their morphologic variants—plasma cells, reactive lymphoid follicles, and lymphoepithelial lesions, CD5-, CD10-immunologic phenotype of neoplastic B-cells, lack of *bcl-2* gene rearrangement) suggest the interpretation of CBCL as the cutaneous counterpart of MALT lymphoma (i.e., skin-associated lymphoid tissue (SALT)-related B-cell lymphoma).^{35,36}

CONCLUSIONS

The current knowledge concerning cutaneous lymphoma allows us to propose a simplified, clinically relevant classification. CTCL is a heterogeneous group, in which clinicopathologic-immunologic entities with therapeutic and prognostic relevance can be reasonably distinguished. CBCL, however, has to be considered a single group, in which clinicopathologic subgroups have no therapeutic and/or prognostic relevance, and are clearly separated from nodal B-cell lymphoma with cutaneous involvement.

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