Primary cutaneous B-cell lymphomas. Current concepts. I.

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A B S T R A C T

Background. Primary cutaneous B-cell lymphoma (pCBCL) has only recently been recognized as a distinct clinicopathologic entity. This entity represents a wide spectrum of lymphoproliferative disorders that must be separated from non-Hodgkin's B-cell lymphomas secondarily involving the skin and cutaneous B-cell pseudolymphomas. They are defined as B-cell lymphomas originating in the skin, with no evidence of extracutaneous disease at presentation, as assessed by adequate staging procedures.

Information Sources. With the advent of improved immunophenotyping and immunogenotyping, increasing numbers of pCBCL cases are being diagnosed. However, there is still confusion regarding the classification, treatment, and prognosis of these patients. The aim of this paper is to provide the clinician with a concise summary of the diagnosis, course, and treatment of pCBCL. Currently, the European Organization for Research and Treatment of Cancer classification is the most adequate classification scheme, identifying the subtypes of pCBCL by clinical behavior and histopathologic findings, and allowing a better management of the patients.

State of the Art. Based on this classification, the most common subtypes of pCBCL are follicular center cell lymphoma and marginal zone B-cell lymphoma, indolent lymphomas with an excellent prognosis (>95% 5-year survival rate in our series). Although local cutaneous recurrences are observed in about 25% of patients, dissemination to internal organs is rare. A less common, specific subtype — the so-called large B-cell lymphoma of the leg(s) — generally has a poorer prognosis, with a 5-year survival rate of approximately 60%.

Perspectives. As a rule, pCBCL is highly responsive to radiation therapy, which should be considered the treatment of choice. Polychemotherapy should be restricted to patients with involvement of several noncontiguous anatomic sites, those refractory or plurirelapsed after radiotherapy, or those with extracutaneous spread.

Key words: cutaneous B-cell lymphomas.

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Non-Hodgkin's lymphomas are a heterogeneous group of tumors that arise from the lymphoreticular system. Approximately 27% of non-Hodgkin's lymphomas occur in extranodal sites, and the skin is the second most common site of extranodal involvement (18%) after the gastrointestinal tract.[1] While in the past decades, a body of knowledge has been collected on the clinicopathologic profile, clinical course and treatment of many entities belonging to the group of cutaneous T-cell lymphomas, our understanding of primary cutaneous B-cell lymphomas (pCBCL) has lagged behind. In fact, studies on series of patients published before 1987 did not distinguish between primary and secondary/concurrent cutaneous presentations of B-cell lymphoma;[2-6] this lack of precision was based upon the common opinion that cutaneous lymphomas other than mycosis fungoides mainly represented dissemination from a nodal disease. On the other hand, cutaneous B-cell disorders clinically characterized by non-aggressive behavior, excellent response to local treatments, and a good prognosis, and histologically showing a *top heavy* distribution of the infiltrate, bland morphology with cytological polymorphism (small and large cells), and reactive lymphoid follicles were constantly regarded as reactive processes (B-cell pseudolymphomas, BCPL).[7-11] Studies of large series of patients, selected on the basis of primary cutaneous presentation of the disease, no evidence of extracutaneous spread, and clonality of neoplastic B-cells,[12-15] documented that pCBCL are indeed a distinct and peculiar group of lymphoproliferative disorders that must be distinguished from non-Hodgkin's B-cell lymphomas with secondary cutaneous involvement and from cutaneous BCPL.

Epidemiology

According to a large body of literature, pCBCL are less frequent than cutaneous T-cell lymphomas, with incidence rates varying considerably between European (ranges from 20% to 25% of all primary cutaneous lymphomas)[16,17] and North American studies (ranges from 3.2% to 7.7%).[18] However, the results of other investigations[19,20] support the evidence that the recently more confident and reliable diagnosis of pCBCL, due to the accuracy of staging procedures and advances in immunophenotyping and immunogenotyping, is the major cause for the increasing incidence of extranodal non-Hodgkin's lymphomas. The crude incidence rate of pCBCL is 0.7 (standardized rate 0.5) per 100,000 inhabitants per year.[19]

Etiology/pathogenesis

At present, there are many unanswered questions concerning the homing of B-cells to the skin and their predilection to stay localized to the cutis in many instances. In fact, there still is no consistent information concerning the existence of a B-cell arm of the skin immune system. In the skin, there are no known equivalents to Peyer's patches of the intestinal tract or Waldeyer's ring of the pharynx. Currently, the only data concern the demonstration that sweat and sebaceous glands synthesize the secretory component of dimeric IgA in humans.[21] However, it has been speculated that the cutis and the draining lymph nodes form an integrated system whereby a lymphoproliferative response to antigenic stimuli may be elicited in the skin.[15] Therefore, pCBCL could represent the neoplastic amplification of this process and could be considered *skin-associated lymphoid tissue (SALT)*-related B-cell lymphomas.[15] In addition, it is thought that the expression of skin-specific homing receptors by normal and/or neoplastic B-lymphocytes in specific situations may explain the preferential circulation to and the accumulation in the skin of lymphoid B-cells. Another speculation concerns the possibility that a combination of etiological factors (infectious, immunologic, and genetic), may play a role in the development of pCBCL. Several infectious agents have been investigated in pCBCL and, in Europe, there is strong evidence implicating *Borrelia burgdorferi*. In fact, *B. burgdorferi*-specific DNA sequences have been demonstrated in a significant minority of pCBCL from European geographical areas with endemic *Borrelia* infections.[22,23] These findings are not confirmed in studies from the United States,[24] and Asia.[25] Recently, molecular analysis of pCBCL documented intraclonal diversity with a high degree of somatic mutations; these data support the hypothesis of an antigen-driven process arising from transformed germinal center B-cells.[26]

Diagnosis

The diagnosis of pCBCL is often quite difficult to make and, given the absence of gold standards, one must take advantage of all the available diagnostic tests (histo-and cytomorphology, immunophenotyping, and genotyping) to arrive at a final decision. A histopathologic diagnosis must be made with caution because of the lack of standards for histological or cytological evaluation. In fact, the histological profile of the various subtypes of pCBCL can be quite similar.

In addition, there is evidence that seems to suggest that low-grade pCBCL and cutaneous lymphoid hyperplasias/BCPL may be part of a spectrum of lymphoproliferative disorders with a step-wise progression from a reactive to a neoplastic state. This can explain why it is sometimes so difficult to differentiate early stages of low-grade pCBCL from cutaneous lymphoid hyperplasias/BCPL.

Classification

There is still controversy regarding the classification of pCBCL. Currently, there are two options for labeling these diseases, the EORTC[16] and WHO[27] schemes, and each of these classifications has its own shortcomings. However, a major advantage of the EORTC classification is that it does classify the entities according to their clinical behavior. In fact, a recent investigation, which compared the applicability of the EORTC and WHO classifications, concluded that the EORTC scheme allows a more precise categorization and better management of patients, especially those affected by pCBCL.[17]

A first main difference between the EORTC scheme and the WHO classification lies in the definition of primary cutaneous follicle center cell lymphoma (FCCL). According to the EORTC scheme, FCCL is a broad term encompassing all lymphomas composed of *follicle center cells, usually a mixture of centrocytes (small and large cleaved follicle center cells) and centroblasts (large non-cleaved follicle center cells with prominent nucleoli*), ranging from the very rare cases with a centroblastic/centrocytic morphology and a follicular pattern of growth to the more frequent cases with a diffuse growth pattern and large cell morphology. Conversely, according to the WHO classification, cutaneous follicle center lymphomas have *a partially follicular pattern and/or are composed of cells that resemble centrocytes (often large) and centroblasts*, and the diffuse follicle center lymphoma (considered to be a rare type of lymphoma) is defined *as a lymphoma composed of cells resembling centrocytes, with a minor component of centroblasts, and an entirely diffuse pattern; both the small and large cell must have the immunophenotype of follicle center cells (typically sIg$^+$, CD10$^+$, bcl-2$^+$, bcl-6$^+$)*. All cases with a large cell

morphology and (generally) a diffuse growth pattern are classified as diffuse large B-cell lymphomas.

A second main difference regards the group of large B-cell lymphomas. In the EORTC scheme, a separate entity distinct from FCCL, and termed large B-cell lymphoma of the leg, is recognized when a B-cell lymphoma predominantly composed of large cells, with centroblastic and/or immunoblastic features, occurs on the leg(s).

Quite recently, a consensus has been reached between representatives of the original EORTC and WHO groups on a new classification of cutaneous lymphomas. This new classification, which will be referred to as the WHO-EORTC classification for cutaneous lymphomas, will be published in the WHO Blue Book series at the end of 2004. In the proposed WHO-EORTC classification three main types of pCBCL are recognized: (i) primary cutaneous marginal zone B-cell lymphoma, (ii) primary cutaneous follicle center lymphoma, and (iii) primary cutaneous large B-cell lymphoma. Histologically, primary cutaneous follicle center lymphoma represents a spectrum of disease and includes lymphomas with follicular, follicular and diffuse, and diffuse patterns of growth. This type of lymphoma is mainly defined according to the criteria used by the EORTC classification for follicle center cell lymphoma, with the exception that rare cases with a monotonous proliferation of centroblasts and immunoblasts (generally showing bcl-2 positivity) not localized on the leg are classified as primary cutaneous large B-cell lymphomas, leg type. This is in agreement with the results of a recent multicenter study documenting that primary cutaneous large B-cell lymphomas with a predominance of round cells have a more unfavorable prognosis than cases with a predominance of large cleaved cells.[28] Primary cutaneous large B-cell lymphomas are diffuse lymphomas with a predominance of large B-cells, in particular centroblasts and immunoblasts. Within this category, primary cutaneous large B-cell lymphoma of the leg(s) is recognized as a distinct entity (primary cutaneous large B-cell lymphoma-leg-type). Primary cutaneous large B-cell lymphomas with a similar histology and immunophenotype which occasionally develop at other sites are recognized as primary cutaneous large B-cell lymphomas, leg type. In addition, the WHO-EORTC classification contains a category *primary cutaneous large B-cell lymphomas, other* which refers to a heterogeneous group of lymphoproliferative disorders which do not belong to the group of primary cutaneous large B-cell lymphomas, leg type, or to the group of primary cutaneous follicle center lymphomas with a diffuse large cell histology. This group includes rare morphological variants of diffuse large B-cell lymphoma with an uncommon morphology, such as anaplastic or plasmablastic subtypes, intravascular large B-cell lymphoma, or T-cell-rich B-cell lymphoma, and/or immunophenotype, clinically not yet well-defined.

In this review, the EORTC classification for cutaneous lymphomas will be used.[16] According to the EORTC scheme, the large majority of pCBCL have been classified as FCCL and only a small proportion as immunocytoma/marginal zone B-cell lymphoma (MZL) or large B-cell lymphoma of the leg.[16] In addition two provisional entities (intravascular large B-cell lymphoma and plasmacytoma) have been included in the EORTC scheme. The term provisional entity refers to pCBCL which display typical histological and immunophenotypic features but lack a distinctive clinical presentation or a defined clinical outcome.

Primary cutaneous follicle center cell lymphoma

Primary cutaneous *FCCL* shows a characteristic clinical presentation consisting in localized, erythematous-to-cyanotic, often mammillated, rarely ulcerated plaques, nodules or tumors of various size frequently surrounded by small papules and slightly infiltrated, figurate plaques, present for months to many years before the onset of larger lesions (Figures 1 and 2). The presence of *satellite lesions* is an important clue for the early diagnosis of the lymphomatous process and its clinical distinction from BCPL (Figure 3). If untreated, skin lesions enlarge over years, but dissemination to extracutaneous sites is very infrequent. Skin lesions usually have a regional distribution (90.6% in our series), preferentially on the trunk (49.6%) and head and neck area (31.8%) and, to a lesser degree, on the limbs (9.2%). Only 9.4% of patients in our series had lesions located in non-contiguous anatomic sites, and presentation with widespread, disseminated lesions was exceedingly rare. There is no sex predilection (M:F=1:1 in our series) and elderly patients are the most frequently affected (mean age at presentation 55 years; median age 58 years; range 22-88 years).

On histological examination, FCCL shows nodular or diffuse infiltrates, with the epidermis almost always spared (Figure 4). The histological picture of a given specimen can be quite variable, and is primarily related to the age and growth rate of the skin lesion.[15] Small and early lesions show patchy-nodular infiltrates located in the upper and mid dermis. The infiltrates are composed of a mixture of small cells with a cleaved nucleus, relatively few large cells with either a cleaved or non-cleaved nucleus, and many reactive T cells. A follicular pattern of growth or its remnants may occasionally be seen in these lesions. If present, neoplastic follicles show germinal centers with clusters of neo-

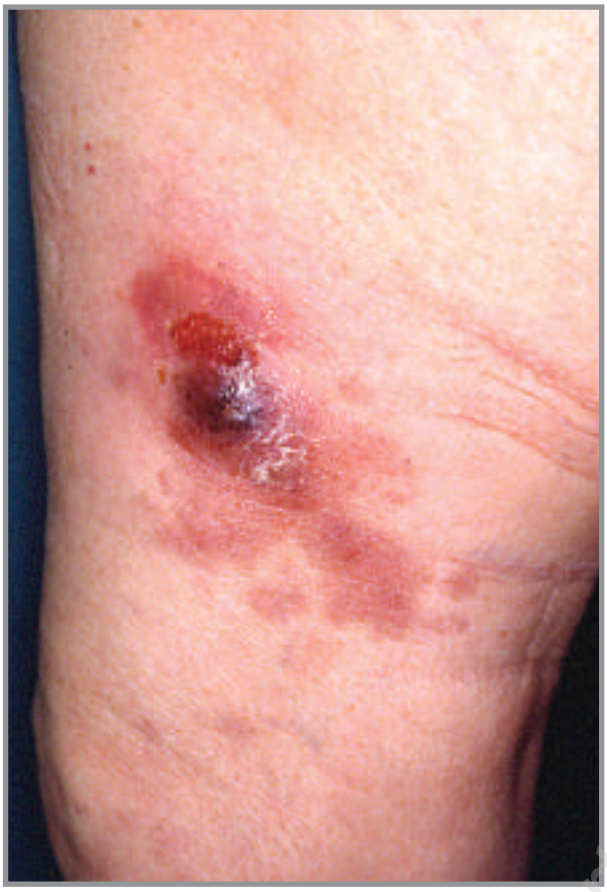

Figure 1. FCCL. Large cyanotic nodule surrounded by slightly infiltrated erythematous plaques on the right thigh of a 71-year old woman.

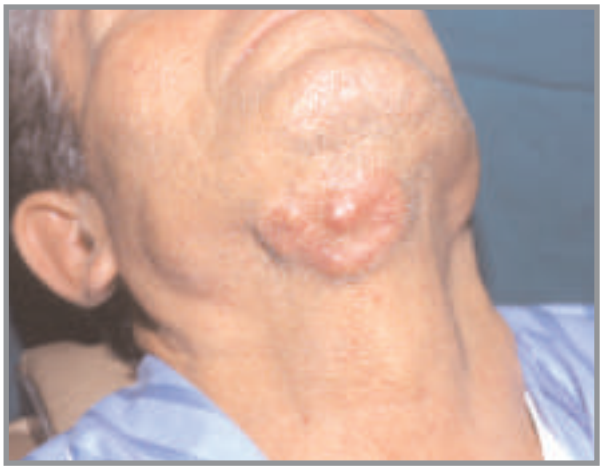

Figure 2. FCCL. Large tumor derived from the coalescence of nodules and plaques on the anterior neck of a 64-year old man.

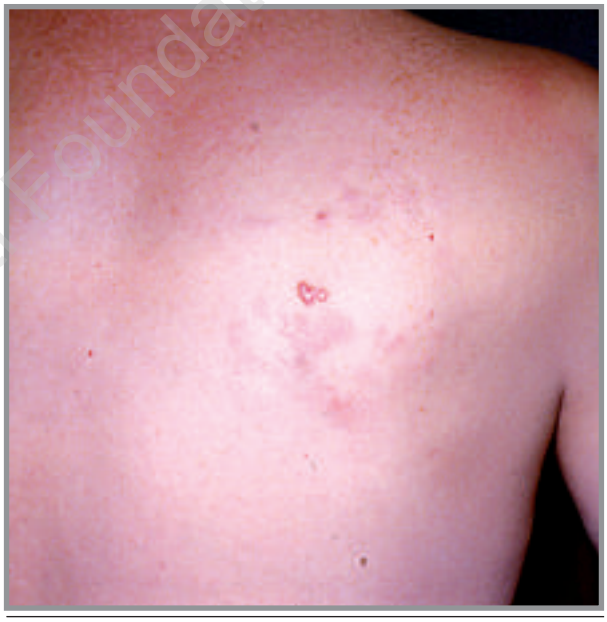

Figure 3. FCCL. Small nodule surrounded by papules and small plaques on the back of a 56-year old man.

plastic bcl-6$^+$ follicle center cells enmeshed in a network of CD21$^+$ and/or CD35$^+$ follicular dendritic cells, are ill-defined, lack starry sky histiocytes, and have a reduced or absent mantle zone. These lesions are classified as centroblastic/centrocytic lymphoma in the updated Kiel classification,[29] as follicular center lymphoma in the REAL classification,[30] and as cutaneous follicle center lymphoma in the WHO classification. Reactive follicle centers and/or their remnants may be observed.

With progression to a tumorous lesions, the lymphoid infiltrates involve the entire dermis, and sometimes the subcutis. Both the number and size of the neoplastic B-cells increase, whereas the number of tumor-infiltrating T-cells decreases. Old and/or rapidly growing tumors quite often show a monotonous infiltrate of large cells, most frequently with cleaved nuclei. Neoplastic follicles are no longer visible except for occasional scattered CD21$^+$/CD35$^+$ follicular dendritic cells. These lesions are classified as one of the subtypes of centroblastic lymphoma in the updated Kiel classification, or as diffuse large B-cell lymphoma in the REAL and WHO classifications. These lesions are not associated with a more aggressive clinical course of the disease.[15]

Tumor cells express B-cell-associated antigens (CD19, CD20, CD22, CD79a) and show monotypic sIg$^+$ (the lack of detectable sIg is common in tumorous lesions with large cell histology). However, monoclonal light chain expression can be masked by polytypic, reactive B-cells, especially in early lesions. Primary cutaneous FCCL consistently expresses bcl-6 while, unlike nodal and secondary cutaneous follicular lym-

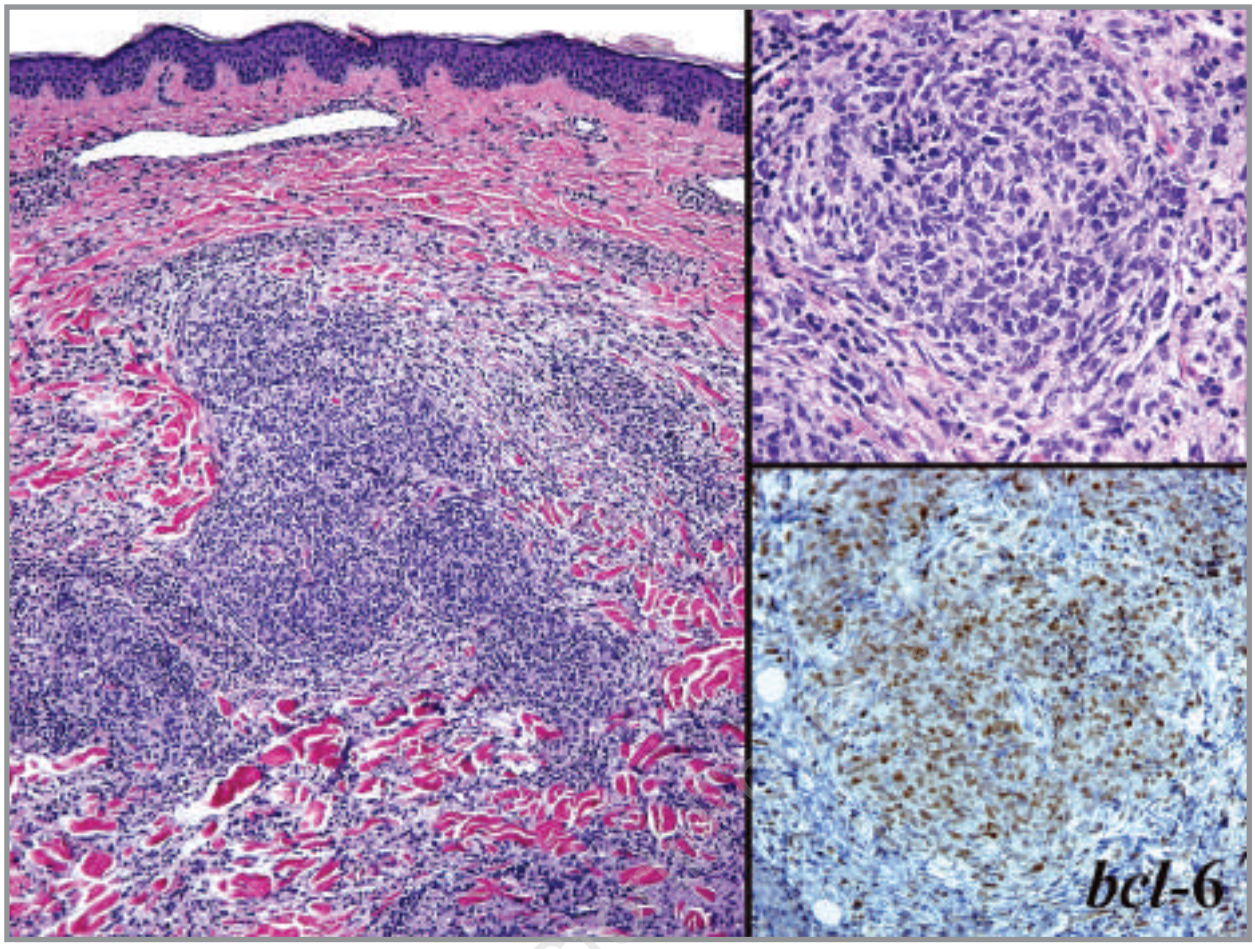

Figure 4. FCCL. Patchy-nodular infiltrates with a tendency to confluence, sparing the epidermis, composed of a mixture of numerous centrocytes and a few centroblasts, with a partially follicular pattern. Tumor cells are strongly bcl-6$^+$ (bottom right).

phoma,[31-33] it does not generally express CD10, very rarely expresses the bcl-2 protein (faint staining), and is not associated with the t(14;18) translocation.[34] In contrast, recent studies, mainly from the USA, reported the presence of t(14;18) translocation as well as bcl-2 expression in cases of primary cutaneous FCCL with a follicular pattern of growth, raising doubts about the existence of phenotypic/genotypic differences between nodal/secondary cutaneous follicular lymphoma and primary cutaneous FCCL.[35-38] The explanation of this discrepancy is still lacking. The estimated 5-year survival is over 95%. Radiotherapy is the treatment of choice. Multiagent chemotherapy is recommended in cases of generalized skin lesions and/or extracutaneous dissemination.

The homogeneous clinical behavior of cases belonging to the FCCL type of cutaneous B-cell lymphoma, irrespective of the architectural pattern (follicular or diffuse) and cellular morphology (predominantly small or large cell), and the absence (in cases classified as either follicular lymphoma or diffuse large B-cell lymphoma, according to the WHO classification) of recurrent chromosomal aberrations, such as translocations affecting *IGH, MYC*, *BCL6* and *MALT1* loci,[39] frequently observed in systemic and diffuse large B-cell lymphomas of the leg(s) (*see below*), are very strong arguments in favor of a holistic conception of FCCL, as advocated by the EORTC classification, and against the splitting of this entity into at least two subgroups, as proposed by the WHO classification.

Immunocytoma/marginal zone B-cell lymphoma

In the EORTC classification, primary cutaneous immunocytoma/marginal zone B-cell lymphoma (MZL) is defined as *a proliferation of small lymphocytes, lymphoplasmacytoid cells, and plasma cells, showing monotypic clg on paraffin sections.* In the updated Kiel classification these lymphomas are termed immunocytomas, while in the REAL and WHO classification

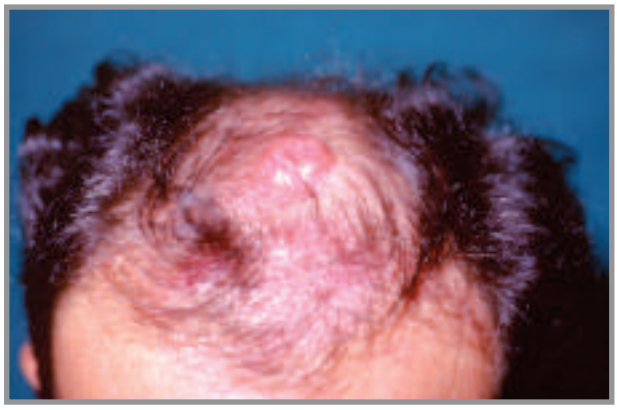

Figure 5. MZL. Erythematous nodule surrounded by slightly infiltrated plaques on the scalp of a 36-year old man.

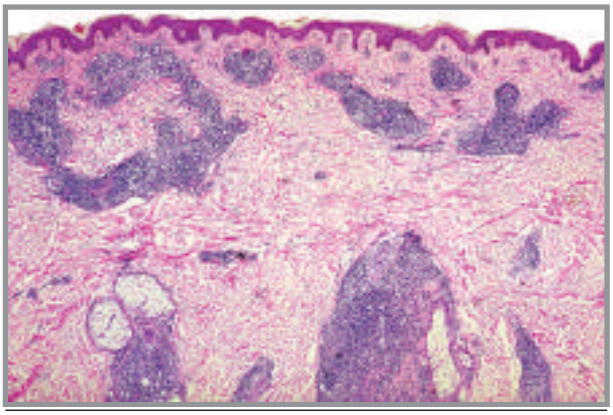

Figure 7. MZL. Nodular infiltrates sparing the epidermis.

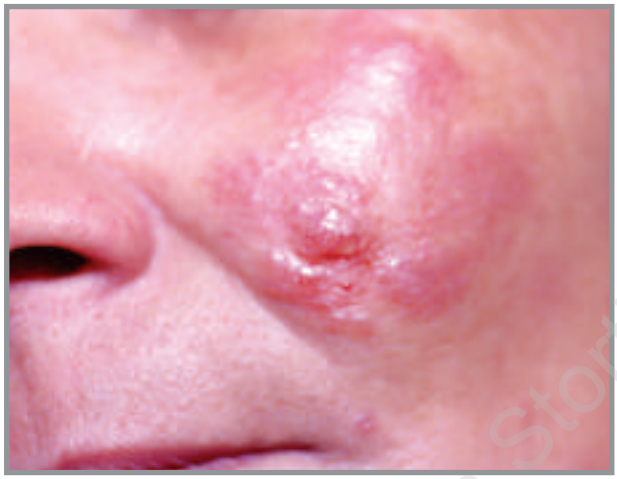

Figure 6. MZL. Large erythematous plaque on the cheek of a 46-year old woman.

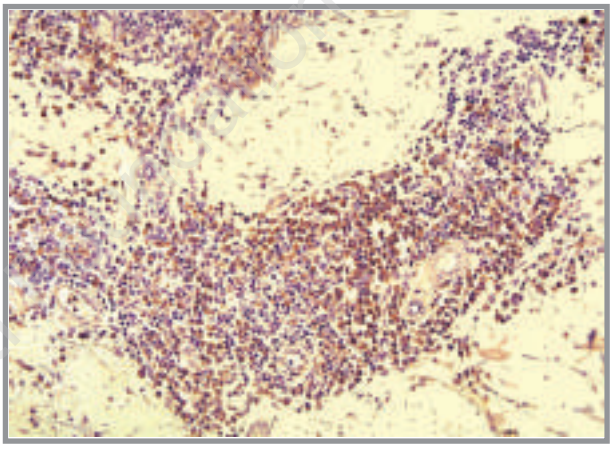

Figure 8. MZL. The neoplastic infiltrate is composed of small lymphocytes, centrocyte-like cells, and plasma cells admixed with a few centroblast-, and immunoblast-like cells. Monotypic (positive) plasma cells are mainly located at the periphery of the infiltrate.

they are classified as extranodal marginal zone B-cell lymphomas or MALT-type lymphomas.

Clinically, MZL presents with features substantially overlapping those of FCCL (Figures 5 and 6), even though some reports emphasize a preferential location on the extremities (arms and legs).[16,40] From the histopathologic point of view, this type of lymphoma is characterized by the presence of nodular or diffuse infiltrates (Figure 7), with the epidermis almost always spared. The infiltrates are composed of small lymphocytes, centrocyte-like cells, and plasma cells admixed with variable numbers of centroblast-, and immunoblast-like cells. The monotypic lymphoplasmacytoid and/or plasma cells are usually located at the periphery of the infiltrates (Figure 8), as they are in MALT-type lymphomas unlike the dispersed distribution of these cells in nodal[29] and secondary cutaneous[40] immunocytomas. This is an additional reason for the present preferred definition of this entity as MZL instead of immunocytoma, as originally proposed by Rijlaarsdam and co-workers.[40] In many cases of MZL, well-evident reactive follicles may be observed. PAS-positive intranuclear or intracellular inclusions are frequently seen. Tumor cells are monotypic clg$^+$, CD79a$^+$, CD5$^-$, CD10$^-$, bcl$^-$6$^-$, bcl-2$^+$. *Borrelia burgdorferi* plays a role in the pathogenesis of some of these lymphomas. MZL has an excellent prognosis; the estimated 5-year survival is over 95%. Radiotherapy is the treatment of choice.

A recent study documented the presence of a novel recurrent translocation involving *IGH* at 14q32 and *MALT1* at 18q21 in about 27% of primary cutaneous MZL. In addition, 33% of the cases harboring t(14;18)(q32;q21) showed trisomy 3 and/or 18, suggesting that this translocation does not occur as the sole genetic abnormality.[41] Conversely, other translocations

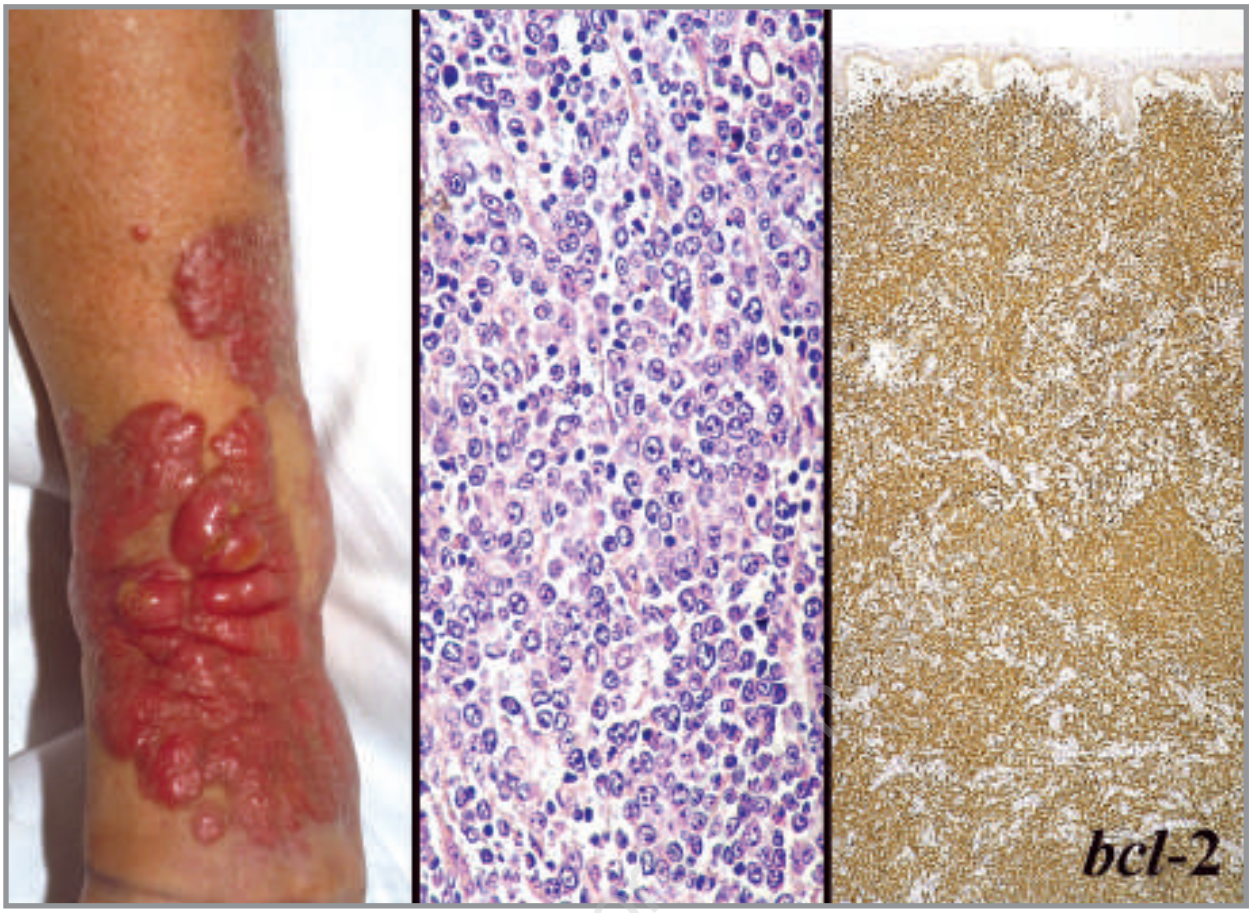

Figure 9. Large B-cell lymphoma of the leg. Large erythematous plaques are located on the left lower leg of a 76-year old woman (left). The diffuse infiltrate is made up of large cells, with centroblastic and immunoblastic morphology, without significant numbers of admixed inflammatory cells (center). Tumor cells strongly express the bcl-2 protein (right).

observed in gastric MALT lymphomas, such as t(11;18)(q21;q21), have not been found in primary cutaneous MZL.

For many years there was intense debate and little consensus regarding the definition of the term MZL and the strict criteria for differentiating this tumor entity from follicular lymphoma in the skin. In fact, there was evidence that many cases classified as FCCL, using the EORTC definition, showed histological characteristics of MALT-type lymphomas when evaluated following the criteria of the WHO scheme.[42] Therefore, emphasizing the heterogeneity of the histological profile of MZL as a typical feature of this type of lymphoma, MZL was proposed as an encompassing term for the very large majority of pCBCL, including over 90% of primary cutaneous FCCL.[43] Indeed, in order to overcome the problem linked to the histologic distinction of FCCL from MZL, and in light of the close similarities in clinical presentation and behavior of FCCL and MZL, it had been proposed to designate these indolent pCBCL with an encompassing term: skin-associated lymphoid tissue (SALT)-related B-cell lymphomas.[44]

Recently, however, it has been documented that immunohistochemistry may furnish valuable help in distinguishing follicular lymphoma from MZL in the skin, especially when lesions have a non-follicular pattern of growth.[35,45] In fact, neoplastic cells in follicular lymphoma consistently express bcl-6 and rarely show CD10 and/or bcl-2 positivity, while tumor cells in MZL are almost constantly bcl-2$^+$, bcl$^-$6$^-$, CD10$^-$. In addition, when follicular structures, or their remnants, are present, immunophenotyping can help in distinguishing reactive follicles (composed of bcl-6$^+$, CD10$^+$, bcl$^-$2$^-$ follicular center cells associated with CD21$^+$ follicular dendritic cells) from follicles colonized by MZL (composed of a variable mixture of bcl-6$^+$, CD10$^+$, bcl$^-$2$^-$ follicular center cells and bcl$^-$6$^-$, CD10$^-$, bcl$^-$2$^+$ tumor cells, associated with CD21$^+$ follicular dendritic cells). Moreover, when a nodular pattern, lacking a distinct

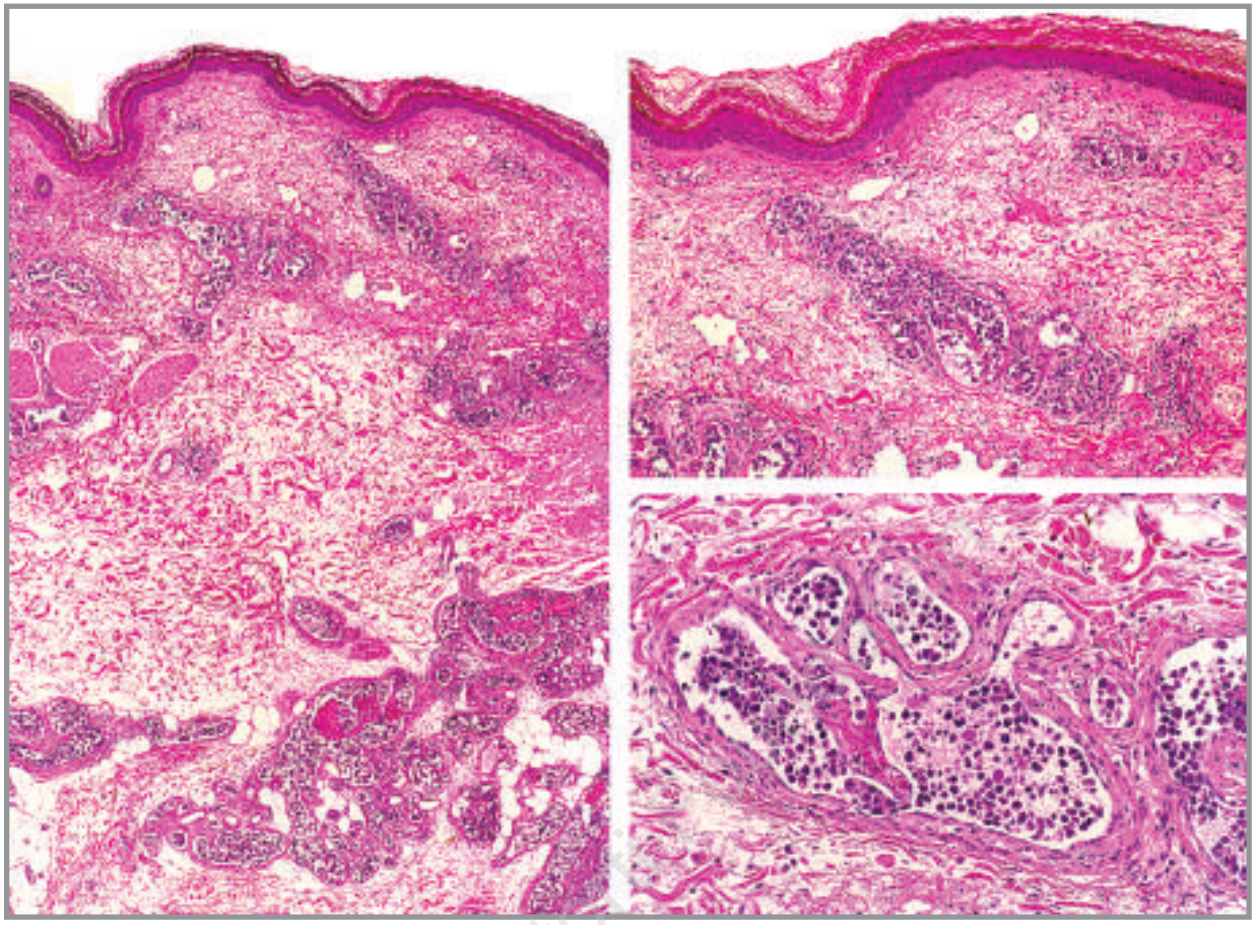

Figure 10. Intravascular large B-cell lymphoma. Accumulation of large neoplastic cells within the dermal blood vessels.

germinal center/mantle zone demarcation is observed in the context of a diffuse pattern of growth, the presence of bcl-6$^+$, CD10$^+$ neoplastic cells in the *interfollicular* areas may help to distinguish between follicular lymphoma and MZL.

Large B-cell lymphoma of the leg(s)

According to the definition of the EORTC classification, primary cutaneous large B-cell lymphoma of the leg is a lymphoma *with a predominance of large B-cells (centroblasts and immunoblasts) presenting on and confined to the leg(s)* (Figure 9). These lymphomas predominantly affect elderly patients. Females are affected more often than males (M:F=1:3-4).[46] Patients present with red or bluish nodules or tumors on one/both lower legs. Histologically, characteristic findings include diffuse non-epidermotropic infiltrates predominantly made up of large non-cleaved B-cells, with variable proportions of centroblast- and immunoblast-like cells. There are few if any admixed small cells and inflammatory cells. More often, the majority of neoplastic cells have the morphology of large non-cleaved follicle center cells, and are classified as one of the subtypes of centroblastic lymphoma in the updated Kiel classification. A few cases show an almost pure population of immunoblasts and are classified as B-immunoblastic lymphoma in the updated Kiel classification. In the REAL and WHO classification these lymphomas are classified as diffuse large B-cell lymphomas. Tumor cells express monotypic sIg and/or cIg, CD19, CD20, CD22, and CD79a. These lymphomas generally strongly express the bcl-2 protein, but are not associated with the interchromosomal t(14;18) translocation. Bcl-6 is expressed by most cases, whereas CD10 staining is generally absent.[45] In the case of solitary or localized skin lesions radiotherapy is preferred; in all other cases multiagent chemotherapy is recommended.

In the experience of the *Dutch Cutaneous Lymphoma Working Group*, the prognosis of these lymphomas is less favorable (estimated 5-year survival 58%) than that of morphologically similar large cell lymphomas

arising on the head and trunk.[46] This more aggressive behavior is still a matter of debate.[42,47-49]

The results of a European multicenter study on primary cutaneous large B-cell lymphomas seem to suggest that the round-cell morphology of the nuclei of tumor cells (R.R.: 8.5; 95% CI: 2.7-27), the location on the leg(s) (RR: 4.2; 95% CI: 1.5-11.5), and the presence of multiple skin lesions (RR: 4.2; 95% C.I.: 1.2-15) are significantly associated with a worse prognosis, and that these elements should be taken into account for a more accurate management of patients.[28] In a recent study by the Scotland and Newcastle Lymphoma Group,[50] disease located on the leg(s) was confirmed to have a poorer prognosis (leg: 67% 5-year disease-specific survival; upper body: 100% 5-year disease-specific survival).

Another recent study on primary cutaneous large B-cell lymphoma of the leg[51] documented that all cases investigated stained for the L-26/CD20cy and CD79a antigens and expressed the bcl-2, bcl-6, and MUM-1/IRF4 proteins but were negative for both the CD10/CALLA and CD138/syndecan-1 antigens. With respect to molecular analysis, the lymphoma population of all these cases carried hypermutation of *Ig* genes, and all but 1 case also harbored mutations of the *BCL-6* gene. These results indicate that primary cutaneous large B-cell lymphoma of the leg has similar morphofunctional and molecular profiles to diffuse large B-cell lymphomas of other sites. As previously mentioned, this concept is additionally supported by the results of a very recent study using interphase fluorescent *in situ* hybridization (FISH), with probes for the *IGH*, *MYC*, *BCL6* and *MALT1* loci, which documented that about 80% of large B-cell lymphomas of the leg harbored breakpoints in at least one of these loci, displaying a pattern of chromosomal translocations similar to that of their systemic counterparts, and quite dissimilar to large cell predominant FCCL.[39] Indeed, in the skin, diffuse large B-cell lymphoma, as defined by the WHO classification and including both large cell predominant FCCL and large B-cell lymphoma of the leg, is not a biologically and clinically meaningful category of lymphoma.

A very recent paper investigated the expression of polycomb-group (*PcG*) genes encoding the HPC-HPH/PRC1 complex in primary nodal and cutaneous large B-cell lymphomas. This study documented that primary nodal large B-cell lymphomas, and secondary cutaneous localizations from such lymphomas, abnormally express the *BMI-1*, *RING1*, and *HPH1 PcG* genes in cycling neoplastic cells. By contrast, tumor cells in primary cutaneous large B-cell lymphomas lacked BMI-1 expression, whereas RING1 was variably detected. Lack of BMI-1 expression was characteristic for primary cutaneous large B-cell lymphomas, because other primary extranodal large B-cell lymphomas originating from brain, testes, and stomach were BMI-1-positive. Expression of HPH1 was rarely detected in primary cutaneous large B-cell lymphomas of the head or trunk whereas it was abundant in primary cutaneous large B-cell lymphomas of the leg(s), which correlates well with this latter's recognition as a distinct clinicopathologic entity. Therefore, clinically defined subclasses of primary large B-cell lymphomas display site-specific abnormal expression patterns of PcG genes of the *HPC-HPH/PRC1 PcG* complex, and some of these patterns (expression profile of BMI-1) may be diagnostically relevant. The distinct expression profiles of *PcG* genes results in abnormal formation of HPC-HPH/PRC1 PcG complexes, and this may contribute to lymphomagenesis and different clinical behaviors of clinically defined large B-cell lymphomas.[52]

Intravascular large B-cell lymphoma

According to the definition of the EORTC scheme, intravascular large B-cell lymphoma, *formerly considered as a vascular proliferation and termed malignant angioendotheliomatosis, is characterized by an accumulation of large neoplastic B-cells within blood vessels*. Patients with this lymphoma present with indurated violaceous patches and plaques, sometimes reminiscent of panniculitis, generally located on the legs or the trunk. Histopathologically, dermal and subcutaneous blood vessels are filled and often dilated by an accumulation of large lymphoid cells, which may cause vascular occlusion. Occasionally, atypical cells can be observed in perivascular areas. Neoplastic cells are CDl9$^+$, CD20$^+$, CD22$^+$, CD79a$^+$, and monotypic sIg$^+$. The estimated 5-year survival is 50%.[16] Multiagent chemotherapy is the treatment of choice. These lymphomas are not listed in the updated Kiel classification and in the REAL scheme, while in the WHO classification they are classified as intravascular large B-cell lymphoma. Intravascular large B-cell lymphomas generally affect the central nervous system and the skin and are characterized by an aggressive clinical course and poor prognosis; cases with cutaneous lesions only seem to have a more favorable clinical behavior. In the forthcoming WHO-EORTC classification, intravascular large B-cell lymphoma will be included in the category primary cutaneous large B-cell lymphoma, other, as a specific subtype.

Plasmacytoma

According to the definition of the EORTC classification, plasmacytoma is an extremely rare type of pCB-CL characterized by *a clonal proliferation of plasma*

cells that develops primarily in the skin (extramedullary plasmacytoma of the skin) without underlying multiple myeloma. Patients show solitary or multiple, smooth, dome-shaped red-to-violaceous nodules; there is no particular site predilection. From the histopathologic point of view, there is a nodular or diffuse dermal infiltrate composed of mature plasma cells. Multinucleated plasma cells and Russel bodies can be documented at times. If prominent atypia or numerous mitoses are present, multiple myeloma should be suspected. On immunophenotyping, tumor cells are monotypic cIg$^+$, CD38$^+$, and usually CD19$^-$ and CD20$^-$. Aberrant reactivity for HMB-45 and cytokeratins has sometimes been documented. Treatments of choice are radiotherapy or surgical excision. The prognosis is excellent with no lymphoma-related death.[16] In the updated Kiel classification and in the REAL scheme, these lymphomas are termed plasmacytoma, while in the WHO classification they are classified as extraosseous plasmacytoma. Indeed, most cases reported in the literature more likely represent reactive plasma cell proliferations or immunocytomas/MZL rather than true plasmacytomas. A workshop organized by the EORTC Cutaneous Lymphoma Task Force on plasma cell-rich cutaneous infiltrates (Bilbao, E, November 30th December 1st, 2001) concluded that most if not all cases of primary plasma cell-rich infiltrate of the skin can probbably be included in the spectrum of MZL or virus/bacteria-linked lymphomas. In agreement with these results, in the forthcoming WHO-EORTC classification, these disorders will be included in the category of primary cutaneous marginal zone B-cell lymphomas.

Miscellaneous rares types [EORTC: not listed]

Two additional types of B-cell lymphoma have been occasionally reported as arising primarily in the skin.

Mantle cell lymphoma is a B-cell lymphoma composed of small-to-medium-sized cells, which closely resemble cleaved center cells (centrocytes), characterized by expression of CD5 and CD43 antigens and bcl-2 and cyclin D1 proteins. On clinical examination, patients present with erythematous plaques or nodules. Almost without exception this type of lymphoma involves the skin secondarily (for this reason it has not been included in the EORTC classification).

T-cell-rich B-cell lymphoma is a lately recognized[53] subtype of diffuse large B-cell lymphoma which is histologically characterized by a dense infiltrate composed of a minor population of neoplastic B-cells (immunoreactive for CD20 and CD79a antigens) in a background of predominant non-neoplastic, polyclonal T cells (expressing T-cell markers such as CD3, CD43, CD45RO). The diagnosis is frequently difficult because the neoplastic B-cell population may be quite sparse, and immunohistochemical and molecular analysis to identify the B-cell origin and clonality of the cells is mandatory. Only 15 cases of primary cutaneous T-cell-rich B-cell lymphoma have been reported worldwide.[54] Patients usually present plaques and/or nodules on the head and neck area or the trunk. There is limited and conflicting information on prognosis. In the forthcoming WHO-EORTC classification, T-cell-rich B-cell lymphoma will be included in the category primary cutaneous large B-cell lymphoma, other.

Conclusions

Primary cutaneous B-cell lymphomas represent a wide spectrum of lymphoproliferative disorders that must be separated from non-Hodgkin's B-cell lymphomas secondarily involving the skin and cutaneous BCPL. Most pCBCL (89.4% in our series of 274 patients) are characterized by a homogeneous clinical presentation (regional extension, 90.6% in our series) and behavior, with good response to non-aggressive treatment modalities (mostly local radiotherapy) and an excellent prognosis (98.5% 5-year survival in our series), despite a significant risk of relapse (24.7% in our series).[48,49]

Classification schemes used for nodal lymphomas are somewhat inadequate for categorizing primary cutaneous lymphomas in a clinically useful way, while the EORTC scheme allows a more precise categorization and better management of patients affected by pCBCL. In particular, in the skin, the category *diffuse large B-cell lymphoma*, as defined by the WHO classification and including both large cell predominant FCCL and large B-cell lymphoma of the leg, is not biologically and therapeutically meaningful. Indeed, separation of large cell predominant FCCL from this group, with its inclusion in the category of FCCL, as advocated by the EORTC scheme, is not only clinically correct and useful for the patients because it prevents them being given unnecessarily aggressive treatments, but is also representative of different incidences of genomic imbalances, possibly indicative of different pathogenetic mechanisms underlying the development of these lymphomas.

It is to be hoped that the forthcoming WHO-EORTC classification for cutaneous lymphomas will finally solve the classification problem. However, at present, given that most data on long-term outcome are based on the EORTC classification, we suggest always considering where a specific entity fits within the EORTC scheme before planning the patient's management.

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