THE SKIN-ASSOCIATED LYMPHOID TISSUE-RELATED B-CELL LYMPHOMAS

The Skin-Associated Lymphoid Tissue-Related B-Cell Lymphomas

Nicola Pimpinelli and Marco Santucci

Primary cutaneous B-cell lymphomas (CBCLs) should be clearly separated from non-Hodgkin's B-cell lymphomas with secondary cutaneous involvement and from cutaneous B-cell pseudolymphomas. The majority of CBCLs are characterized by a homogeneous clinical presentation and behavior, with good response to local radiotherapy, low tendency to extracutaneous spread, and excellent prognosis. According to the European Organization for Research on the Treatment of Cancer classification of primary cutaneous lymphomas, CBCLs with an indolent behavior are divided into 2 subgroups: follicular center cell lymphoma and immunocytoma/marginal zone lymphoma, due to putative histologic similarities with their purported nodal counterparts. In addition, a third subgroup with intermediate prognosis (large B-cell lymphoma of the leg) is identified. Conversely, the identification of distinct subgroups is disputable from a strictly histologic, immunophenotypic, and genotypic point of view, and has neither correlation with the clinical course nor the prognosis of the disease. Moreover, the majority of CBCLs show a uniform immunophenotype (CD5−, CD10−) and genotype (lack of bcl-1/bcl-2 and c-myc gene rearrangement) of neoplastic cells. Therefore, we favor the use of the term Skin-Associated Lymphoid Tissue (SALT)-related B-cell lymphomas, due to the close similarities between CBCLs and mucosa-associated lymphoid tissue (MALT) lymphomas, and the evidence for an acquired B-cell arm of SALT.

ALTHOUGH PRIMARY cutaneous B-cell lymphomas (CBCLs) have been recognized since 1978,[1,2] studies on patients published before 1987 did not distinguish between primary and secondary/concurrent cutaneous presentations.[3-7] This is based on the common opinion that cutaneous lymphomas, other than mycosis fungoides, represented dissemination from nodal disease. Conversely, B-cell cutaneous disorders characterized clinically by indolent behavior, good response to local treatment, and favorable prognosis and histologically by "top heavy" distribution of the infiltrate, cytologic polymorphism (small and large cells), and the presence of lymphoid follicles were invariably regarded as reactive processes (B-cell pseudolymphomas [B-PLs]).[2,8-11]

Studies of large groups of patients—carefully selected on the basis of primary cutaneous presentation, no evidence of extracutaneous disease, and monoclonality of neoplastic B cells[12-15]—demonstrated that CBCLs are indeed a distinct group of lymphoproliferative diseases that should be distinguished from non-Hodgkin's B-cell lymphomas with secondary cutaneous involvement and from cutaneous B-PLs.

The majority of CBCLs are characterized by a homogeneous clinical presentation and behavior, with good response to nonaggressive treatments (mostly local radiotherapy), a low tendency of extracutaneous spread, and excellent prognosis, so that they have been defined as semimalignant ("pseudolymphomatous").[16] On the basis of the "classic" interpretation proposed by the Dutch Cutaneous Lymphoma Working Group (DCLWG),[17] this large group of CBCLs are currently classified as follicle center cell lymphoma (FCCL)[12,18] and immunocytoma (IC)[19] or marginal zone lymphoma (MZL),[20,21] according to the recently published European Organization for Research and Treatment of Cancer (EORTC) classification of primary cutaneous lymphomas.[22]

Indeed, on the basis of the close similarities with mucosa-associated lymphoid tissue (MALT) lymphomas[23] and the evidence for an acquired B-cell arm of the skin-associated lymphoid tissue (SALT), we proposed the designation of these CBCLs as SALT-related B-cell lymphomas.[24] This term, which encompasses the "traditional" histologic categories (FCCL and IC/MZL), should be regarded both as a concept and as a diagnostic category. This article will show the clinical, histologic, immunophenotypic, and molecular bases of our interpretation.

The clinicopathologic significance of a smaller group of CBCLs (so-called primary cutaneous large B-cell lymphoma of the leg),[25] characterized by: (1) rapid growth of skin lesions; (2) large cell histology, high proliferation rate, and bcl-2 protein expression by neoplastic cells at presentation; and (3) possible predi-

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1085-5629/00/1902-0009$10.00/0

doi:10.1053/sder.2000.8332

lection for the elderly (>70 years) and selected skin sites (lower legs) are briefly discussed in this article and extensively met in the article "Primary Cutaneous Large B-Cell Lymphomas" by Wechsler and Bagot on page 130 in this issue.

CLINICAL FEATURES

The majority of patients affected by CBCLs show a characteristic clinical presentation: localized, erythematous to cianotic, sometimes mammillated, rarely ulcerated plaques, nodules, or tumors of various size are very often surrounded by small papules and slightly infiltrated, sometimes figurate plaques (Figs 1 and 2), which are present for months to years before the appearance of larger lesions. The presence of the aforementioned "satellite" lesions surrounding the "main" lesion(s) can be an important clue in the early diagnosis of CBCLs and their clinical differentiation from B-PLs. Conversely, the differential diagnosis between CBCLs and B-PLs can be very difficult clinically when only isolated nodules or plaques, especially small ones (this presentation, although infrequent, is not exceptional), are present. Skin lesions usually have a regional distribution (88.7% in our series of 186 patients), preferentially on the trunk (51.2%), head and neck (23.3%) and, to a lesser extent, on the limbs (14.2%). Only 11.3% of patients had lesions located in noncontiguous anatomic sites, and the presentation with widespread, disseminated lesions is exceedingly rare in CBCLs. We did not observe any particular gender predilection in our study (97 males, 89 females). The median age was 59 years (range 22-88).

HISTOLOGIC, IMMUNOPHENOTYPIC, AND MOLECULAR FEATURES

Presently it is clear that a "low grade" histologic picture is an incorrect and unreliable criterion to differentiate between CBCLs and B-PLs. The only reliable tool is the demonstration of B-cell monoclonality by immunohistochemistry (Fig 3) and/or molecular analysis by Southern blotting or polymerase chain reaction.[26-31]

It is indeed difficult to categorize CBCLs according to the updated Kiel classification[32] or the Revised European-American Lymphoma (REAL) classification.[33] However, the approaches to a specific classification are slightly different at present. The classification for CBCLs recently proposed by the Cutaneous Lymphoma Study Group of the EORTC,[22] mainly based on the experience of the DCLWG,[17] distinguishes clinicopathologic entities with indolent course (FCCL and IC/MZL) from another with an intermediate course (so-called primary cutaneous large B-cell lymphoma of the leg)[33]; in addition, rare and undefined types are listed in the EORTC classification.

Primary cutaneous FCCL and IC/MZL, which affect more than 90% of all patients with a definite diagnosis of CBCL, share a good response to radiotherapy with a generally excellent prognosis and behave much better than morphologically similar lymphomas in the lymph nodes. Primary cutaneous FCCL[12,18] is characterized by regional lesions mainly located on the trunk and scalp. Histologically, it is composed of cells reminiscent of the morphologies of FCCL, usually a mixture of small and large cleaved cells (putative centrocytes) and large cells with prominent nuclei and nucleoli (putative centroblasts and immunoblasts). It has a chronic course, is highly sensitive to radiotherapy, and has a good prognosis. Primary cutaneous IC[19] is clinically characterized by one or several, often deeply seated, nodules or tumors, is almost without exception located on arms or legs, and has an excellent prognosis. Histologically, lymphoplasmacytoid/plasma cells are located at the periphery of the nodular infiltrates, different from the dispersed distribution of the same cells in secondary cutaneous IC and nodal IC[32] (this is the main reason why other groups have suggested to define this entity as MZL).[20,21] The identification of primary cutaneous large B-cell lymphoma of the legs, a rare subtype of CBCLs, is also mainly based on the DCLWG experience.[25]

Some investigators have hypothesized that most CBCLs are indeed marginal cell (parafollicular/monocytoid) lymphomas, and that this is the reason for their good prognosis as opposed to the rare, "true" primary cutaneous FCCLs.[34] Nevertheless, the striking tendency to remain localized and the very rare occurrence of bone marrow involvement differentiate CBCLs, similar to MALT lymphomas, from marginal cell (monocytoid/parafollicular) lymphomas and justify their designation as distinct entities.

An Alternative View: The SALT Hypothesis

Since 1988 at the International Symposium on Cutaneous Lymphoma held in Copenhagen,[35] and later, based on a larger study of patients,[15] we stressed the close similarities between CBCLs, morphologically classifiable either as so-called primary cutaneous FCCL or as IC/MZL, and B-cell lymphomas of MALT.[23,36] The majority of CBCLs show: (1) nonaggressive clinical behavior (localized disease, good response to orthovolt radiotherapy, low tendency to extracutaneous spread, and excellent prognosis); (2) subtle histologic differences, both in terms of cellular morphology and architectural organization of the different cell types, from "true" FCCLs and IC of the lymph nodes, so that their classification either as FCCLs or IC is a strained categorization; (3) tumor cells with unimodal morphometric features intermediate between those of centrocytes and centroblasts of nodal FCCLs (tumor cells are

not "true" centrocytes or centroblasts)[37]; (4) characteristic polymorphism of the neoplastic cellular infiltrate, with cells showing a fluent transition of shapes and sizes and resembling small centrocytes (centrocyte-like cells),[23] large anaplastic centrocytes, centroblasts of different subtypes, plasma and/or plasmacytoid cells, and immunoblasts (Fig 4). The relative proportion of each of these cell types and the extent of the reactive T-cell and B-cell infiltrate (often represented by reactive lymphoid follicles) are highly variable according to the size, age, and growth rate of lesions and do not have any significant correlation with the overall evolution of the disease.[15] A prevalence of centrocyte-like B cells, plasma/lymphoplasmacytoid cells, and an abundant, often overwhelming, infiltrate of small lymphocytes (mostly T cells) are characteristic features of early lesions, while a clear-cut prevalence of large blast-like cells and a scarce reactive infiltrate are the rule in late lesions. It is typical to find different histologic features (low grade and high grade) in different lesions in the same patient (Fig 5) and even in different areas of the same lesion (discordant/composite picture); (5) multiphasic histologic features, with the various cell types often grouped together rather than intermingled; (6) lymphoepithelial lesions (an occasional finding in CBCLs, different from MALT lymphomas); (7) very frequent CD5−, CD10− phenotype of neoplastic B cells; (8) nerve growth factor receptor+, CD14−, CD21 ± phenotype of associated dendritic cells[38]; (9) lack of either t(11;14)/t(14;18) translocation or bcl-1/bcl-2 gene and c-myc oncogene rearrangements.[39,40] Bcl-2 protein expression, usually absent in B-PLs,[39] is significantly more frequent in secondary than in primary CBCL.[39,40] In addition, the relationship between bcl-2 expression and bcl-2 gene rearrangement is definitely closer in secondary than in primary CBCL.[39,40]

The aforementioned histologic and, more importantly, phenotypic and genotypic features led us to hypothesize a possible common histogenesis for CBCLs, in analogy with that proposed for MALT lymphomas[23,36] and so-called parafollicular/monocytoid lymphomas.[41] The previously described histologic, immunophenotypic, and genotypic features argue against a "true" FCCL nature of tumor cells, and may be reasonably interpreted as indicative of an origin from a cell type capable of differentiation into the various cell morphologies (centrocyte-like, centroblast-like, immunoblast-like) observed in CBCLs as well as MALT lymphomas and parafollicular/monocytoid lymphomas.[42]

TREATMENT AND PROGNOSIS

Skin lesions are highly responsive to local radiotherapy (RT).[15,43-45] Indeed, most leading investigators currently agree that RT should be considered the elective treatment for most CBCLs. Concerning the most suitable techniques and the recommended doses, local orthovolt RT (LoRT) guarantees very good results,[43,44] although electron beam and photon beam can also be used successfully.[45] We have been using LoRT (half-deep x-rays, contact x-rays, soft x-rays) for the last 2 decades, with excellent results, according to the following protocol: potency range 50 to 120 kV, single dose per field 2.5 to 5 Gy, total dose of 15 to 25 Gy delivered in 2 to 3 weeks in 4 to 8 fractions, irradiation fields (up to 20 cm in diameter) almost invariably including 1 to 2 cm of healthy skin around the lesions. In particular, the slightly infiltrated erythematous patches and plaques surrounding the larger nodules or tumors have to be included in the irradiation field. LoRT produced a complete remission in 98.2% of 115 patients treated at presentation, with residual slight erythema and pigmentation. Small, isolated lesions can be surgically excised, with or without additional RT. Only rare patients with disseminated lesions, multiple relapses after RT, and, of course, those experiencing extracutaneous spread of disease should be treated at presentation with multiagent chemotherapy (cyclophosphamide, vincristine, prednisone [COP-] and cyclophosphamide, adriblastine, vincristine, prednisone [CHOP]-like regimens).[15,43,45]

The relapse rate is 26.3% in our study, with a disease-free interval ranging from 3 to 134 months (median 42). Most relapses are limited to the skin, very often outside the previously irradiated area and can be successfully retreated with LoRT. Extracutaneous spread is quite rare (8.9% in our series), with an excellent actuarial survival rate (98.3% and 95.6% at 5 years and 10 years, respectively). No significant differences were found in our study between disease-free period and/or relapse rate on one hand, and radiation dose, anatomic site, gender, age, histoarchitectural pattern (Fig 6), and/or cellular morphology of the infiltrating cells on the other hand. In particular, the small group of patients in our study with large B-cell lymphoma "de novo" (18 patients) did not show any significant difference in overall survival (88.9% at 5 years) as compared to the strikingly larger group of CBCLs having the characteristic clinicopathologic features of SALT-related B-cell lymphoma, notwithstanding the rapid growth of skin lesions, high proliferation rate, strong bcl-2 protein expression by neoplastic cells at presentation, predilection for the elderly (>70 years), and selected skin sites (lower limbs).

CONCLUSION

CBCLs represent a distinct group of lymphoproliferative diseases; they have to be clearly separated from non-Hodgkin's B-cell lymphomas with secondary cutaneous involvement and from cutaneous B-PLs. The majority of CBCLs are characterized by a homogeneous clinical presentation and behavior, with good response to LoRT, a low tendency to extracutaneous spread, and

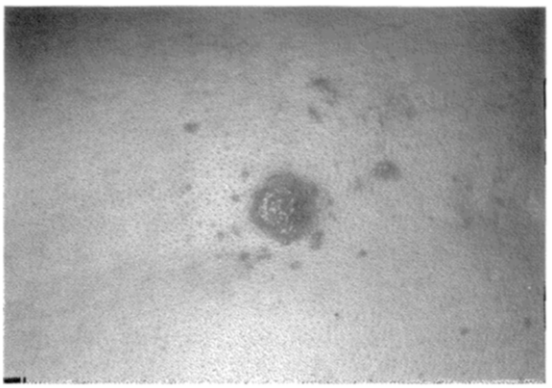

Fig 1. Erythematous nodule surrounded by small papulo-nodular lesions on the back of a male patient.

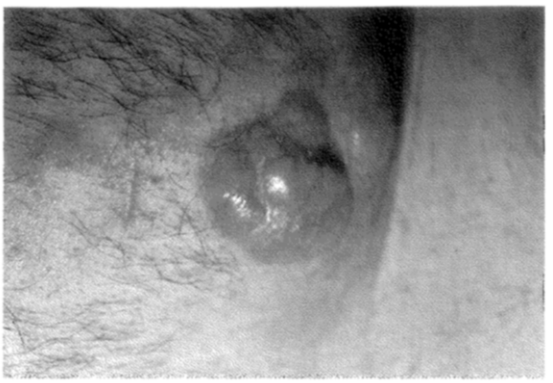

Fig 2. Large mammillated nodule surrounded by slightly infiltrated plaques and papulo-nodular lesions on the right mammary region of a male patient.

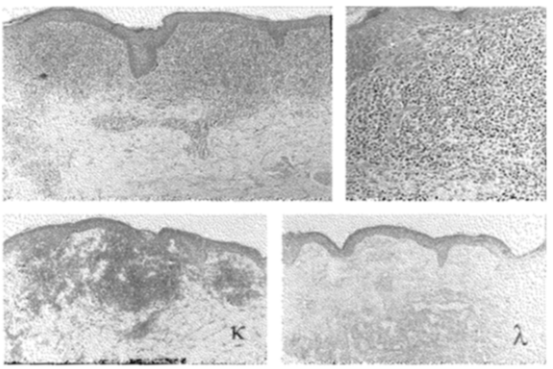

Fig 3. This figure emphasizes the crucial role of the demonstration of monoclonality by immunohistochemistry in the proper identification of CBCLs, and their distinction from B-PLs and inflammatory dermatoses.

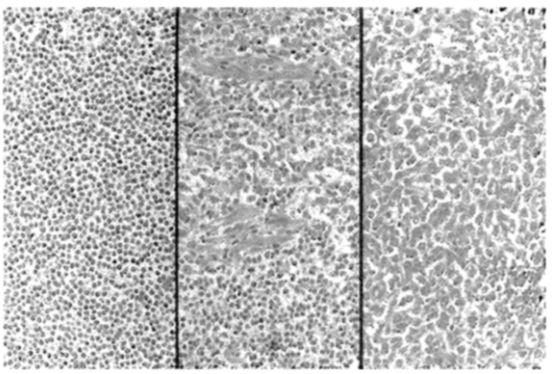

Fig 4. Range of appearances of neoplastic cells in CBCLs.

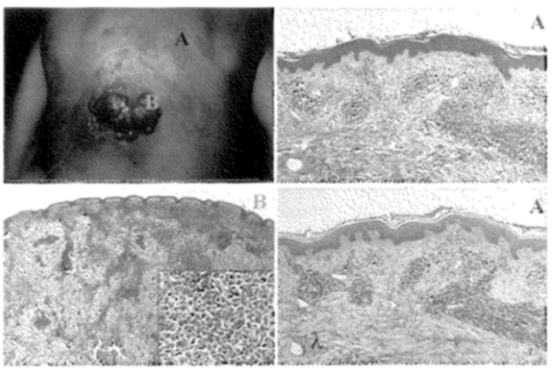

Fig 5. Typical clinical picture of CBCLs (top left). Biopsies performed in 2 different lesions of this patient evidenced different morphologies, indicating the continuum existing between the so-called cutaneous IC/MZL (A; top right hematoxylin and eosin, bottom right anti-λ) and (B) the so-called cutaneous FCCL and making questionable the identification of histologic subgroups in CBCLs.

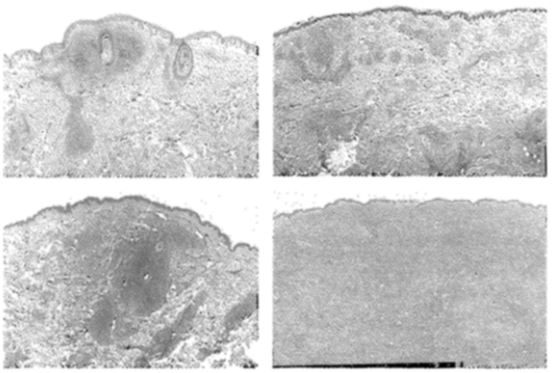

Fig 6. Histoarchitectural patterns of the infiltrate in CBCLs. The nodular pattern (top left and right) is typical of young lesions (aged <3 months). The diffuse pattern (bottom right) is characteristic of old lesions (aged >12 months). The mixed pattern (bottom left), although not characteristic of any specific age of lesion, is the most frequently observed.

excellent prognosis.[15,46,47] The close similarities between CBCLs and MALT lymphomas, and the evidence for an acquired B-cell arm of SALT prompted us to designate these CBCLs as SALT-related B-cell lymphomas.[24,46-48]

A matter of further debate is whether the rare, so-called large B-cell lymphoma of the leg, the third subgroup of primary CBCL identified in the EORTC classification,[22] should indeed be regarded as a distinct clinicopathologic entity.[49] In this regard, an EORTC multicenter study, chaired by the French Cutaneous Lymphoma Study Group, is ongoing. The preliminary results of the study suggest that old age (>70 years) and de novo "round" large cell histology (noncleaved cells, ie, centroblast-) (and immunoblast-like cells) are indeed significantly related to a worse prognosis in a multivariate analysis, while the lower limb location is not.[50]

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