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Primary cutaneous B-cell lymphoma: A clinically homogeneous entity?

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Primary cutaneous B-cell lymphomas (CBCLs) represent a distinct group of lymphoproliferative diseases that have to be distinguished from non-Hodgkin's B-cell lymphomas with secondary cutaneous involvement and from cutaneous B-cell pseudolymphomas.

PRIMARY CBCL

Although several cases of primary CBCL had been reported by 1978,¹⁻⁴ studies published before 1987 did not distinguish between primary and secondary/concurrent cutaneous presentations.⁵⁻¹⁰ This was based on the common opinion that cutaneous lymphomas other than mycosis fungoides represented dissemination from nodal disease. On the other hand, B-cell cutaneous disorders characterized clinically by good response to local treatment and favorable prognosis and histologically by cytologic polymorphism (small and large cells) and the presence of lymphoid follicles were regarded as reactive processes (pseudolymphomas).^{4,11-14} Since 1987, studies of patients with primary CBCL have been published,¹⁵⁻¹⁸ in which the patients were carefully selected on the basis of (1) primary cutaneous presentation, (2) no evidence of extracutaneous disease, and (3) light chain monoclonal restriction or negative staining for surface immunoglobulins on CD20⁺, CD22⁺ B cells in frozen sections or immunoglobulin heavy chain gene rearrangement, or both. These patients had characteristic clinical features: localized plaques, nodules or tumors, often surrounded by

papules and slightly infiltrated, sometimes figurate plaques, present for months to many years before the appearance of larger lesions. These lesions usually have a regional distribution on the trunk (51.7% in our series of 154 patients to date) and head and neck (23.1%) and, to a lesser extent, on the limbs (13.3%). Skin lesions are highly responsive to orthovolt radiotherapy¹⁸⁻²¹ (96.9% complete remissions in our series), either at presentation or after relapse. Despite cutaneous relapses (25.8% in our series), primary CBCLs have only a slight tendency to extracutaneous spread (9.1% in our series) and an excellent prognosis (96.2% 5-year and 95.5% 10-year survival in our series). However, it is now clear that a favorable clinical course and a "low-grade" histologic picture are incorrect and unreliable criteria to differentiate between CBCL and pseudolymphomas. The only reliable tool is the demonstration of B-cell monoclonality by immunohistochemistry and/or molecular analysis by Southern blotting and the polymerase chain reaction.^{18,22-28}

The conclusion that most primary CBCLs have highly distinctive clinical features, first proposed by the Dutch Cutaneous Lymphoma Working Group (DCLWG)¹⁵ and two Italian groups (Milan¹⁶ and Florence^{17,18}) and later ratified at the First International Symposium on Cutaneous Lymphoma in 1988,^{24,29,30} is now shared by other groups worldwide, particularly in Europe. Nevertheless, an interesting and stimulating debate is ongoing about the classification, histogenesis, and pathogenesis of primary CBCL. There is consensus concerning the difficulty in categorizing primary CBCL according to the updated Kiel classification³¹ or to the Revised European-American Lymphoma (R.E.A.L.) classification.³² However, the proposed solutions are different.

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CLASSIFICATION OF PRIMARY CBCL: THE DCLWG VIEW

The DCLWG proposed classifying primary CBCL into clinically low-grade (follicular center cell [FCC] lymphoma and immunocytoma [IC]) and rare/undefined types.³³ Primary cutaneous FCC lymphoma and IC, which affect more than 90% of all patients with a definite diagnosis of primary CBCL, share a good response to radiotherapy and a generally excellent prognosis that is much better than morphologically similar lymphomas in lymph nodes. Primary cutaneous FCC lymphoma^{15,34} is characterized by localized infiltrative lesions on the trunk and scalp and, in elderly patients, on the legs. Histologic examination reveals that it is composed of FCCs, usually a mixture of centrocytes (small and large cleaved FCC) and centroblasts (large FCC with prominent nucleoli). It has a chronic course, is highly sensitive to radiotherapy, and has a good prognosis, with the exception of a recently defined subset (large-cell FCC lymphoma of the leg), which predominantly affects elderly patients and has an intermediate prognosis.³⁵ Primary cutaneous IC³⁶ is characterized clinically by one or several, often deeply seated nodules or tumors, almost without exception on arms or legs, and has an excellent prognosis. Histologic examination reveals lymphoplasmacytoid/plasma cells at the periphery of the nodular infiltrates, different from the dispersed distribution of the same cells in secondary cutaneous IC³⁶ and nodal IC.³¹

AN ALTERNATIVE VIEW: THE SALT/MALT HYPOTHESIS

Since 1988, at the International Symposium on Cutaneous Lymphoma held in Copenhagen²⁹ and later based on our series of patients,¹⁸ we stressed the close similarities between primary CBCL, morphologically classifiable as FCC lymphomas or IC, and B-cell lymphomas of the so-called mucosa-associated lymphoid tissue (MALT lymphomas).³⁷ These have nonaggressive clinical behavior, with mostly localized disease, a good response to orthovolt radiotherapy, only a slight tendency to extracutaneous spread, and an excellent prognosis. In our experience¹⁸ and in that of other groups (Berti E., unpublished data), a distinct subset of elderly patients characterized by lesion location on the legs, large-cell histology

findings and intermediate prognosis³⁵ is not identifiable. Histologic features of primary CBCL include a characteristic polymorphism of the neoplastic cellular infiltrate, with cells resembling small centrocytes ("centrocyte-like cells"³⁷), large anaplastic centrocytes and centroblasts of different subtypes, plasma and/or plasmacytoid cells, and immunoblasts. 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.¹⁸ 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, whereas a clear-cut prevalence of large blastlike cells and a scarce reactive infiltrate are characteristic of late lesions. It is typical to find different histologic features (low-grade and high-grade) in different lesions in the same patient and even in different portions of the same lesion.¹⁸ MALT lymphomas and primary CBCLs also share multiphasic histologic features, with the various cell types often grouped together rather than intermingled; lymphoepithelial lesions, although this is an occasional finding in primary CBCL; phenotype of neoplastic B cells (CD5⁺, CD10⁻); and genotype of neoplastic B cells, which do not show either t(11;14)/t(14;18) translocation or bcl-1/bcl-2 gene and c-myc oncogene rearrangements.^{23,24,38,39} Bcl-2 expression is never detected in B-cell pseudolymphomas³⁸ and is significantly more frequent in secondary CBCL (nodal FCC lymphomas with secondary cutaneous involvement) than in primary CBCL^{38,39}; in addition, the relation between bcl-2 expression and bcl-2 gene rearrangement is definitely closer in secondary CBCL than in primary CBCL.^{38,39} These findings suggest the possible significance of bcl-2 protein expression and bcl-2 genes rearrangement to differentiate between B-cell pseudolymphomas, primary CBCL, and secondary CBCL.

The above histologic and, more important, phenotypic/genotypic features led us to hypothesize a possible histogenesis from the marginal cell for primary CBCL,^{40,41} similar to what has been proposed for MALT lymphomas^{37,42} and so-called

parafollicular/monocytoid lymphomas.⁴³ Several facts argue against an FCC origin and may be reasonably interpreted as indicative of origin from the marginal cell. This cell type is putatively capable of differentiation into the various cells characteristic of most primary CBCLs as well as of MALT lymphomas and parafollicular/monocytoid lymphomas.⁴⁴ The facts that primarily argue against an FCC origin are as follows: (1) the CD5⁺, CD10⁺, Leu-8⁺ phenotype of neoplastic B cells; (2) the nerve growth factor receptor + (clone 20.4), CD14⁺, CD21⁺ phenotype of associated dendritic cells⁴⁵⁻⁴⁷; (3) the lack of t(11;14)/t(14;18) chromosomal translocation and bcl-1/bcl-2 genes and c-myc oncogene rearrangement; and (4) the demonstration, in a series of cases diagnosed as cutaneous FCC lymphomas, of a unimodal population of cells with intermediate morphometric features, which could not be identified as centrocytes, centroblasts, or immunoblasts.⁴⁸ Some authors have hypothesized that most primary CBCLs are indeed marginal cell (parafollicular/monocytoid) lymphomas and that that is the reason for their good prognosis as opposed to the rare, true FCC lymphomas.⁴⁹ Nevertheless, the striking tendency to remain localized and the rare occurrence of bone marrow involvement make primary CBCLs and MALT lymphomas different from marginal cell (monocytoid/parafollicular) lymphomas and justify their designation as distinct entities. Similarly, some question the classification of a certain proportion of primary CBCLs as cutaneous IC, notwithstanding the presence of monotypic plasma/lymphoplasmacytoid cells. In fact, in the skin the plasma/lymphoplasmacytoid cells are generally located at the periphery of the nodular infiltrates and differ from the dispersed distribution of the same cells in secondary cutaneous IC³⁶ and nodal IC.³¹ Conversely, in MALT lymphoma the plasma/lymphoplasmacytoid cell monoclonal proliferation can be marked and usually surrounds islands of centrocyte-like cells.⁴³

The many striking similarities between MALT B-cell lymphoma and primary CBCL suggest that most of the latter may be reasonably considered the cutaneous equivalent of MALT lymphoma and the neoplastic counterpart of the acquired B-cell skin-associated lymphoid tissue (SALT),^{18,49} which is the development of cutaneous B-cell hyperplasia in relation to known stimuli (insect

bites, tattoos, *Borrelia burgdorferi* infection) and the potential of some to progress to overt lymphomas.^{26,50,51} For these reasons, we proposed the term *skin-associated lymphoid tissue* (SALT)-related B-cell lymphoma.^{18,29,40,41}

These interpretations strongly contrast with those of the DCLWG.⁵² They state that the marginal cell hypothesis is only related to "negative" criteria and that a reliable "positive" marker is currently lacking (a monoclonal antibody, KiM1p, has been recently proposed as a possible diagnostic tool by the Graz group^{53,54}). For this reason, the DCLWG considers their current classification of primary CBCL based on the delineation of well-defined clinicopathologic entities (FCC lymphoma, with the large-cell variant of the leg, and IC, plus other rare types) to be the most reliable.

CONCLUSION

Primary 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-cell pseudolymphomas. Most primary CBCLs are characterized by a homogeneous clinical presentation and behavior, with good response to orthovolt radiotherapy, only a slight tendency to extracutaneous spread, and excellent prognosis.^{33,55} For this reason, bizarre terms such as semimalignant ("pseudolymphomatous") CBCLs⁵⁶ have recently been coined. The DCLWG strongly suggests classifying these primary CBCLs as FCC lymphoma and IC.³³ In our series, the large majority of primary CBCLs have a uniform immunophenotype (CD5⁺, CD10⁺) and genotype (lack of bcl-1/bcl-2 and c-myc gene rearrangement) of neoplastic cells, despite a great histologic and immunohistologic variability largely related to the age and growth rate of the skin lesions, without any significant correlation with the overall evolution of the disease. These similarities to MALT lymphomas and the evidence for an acquired B-cell arm of SALT led us to propose the designation of these CBCL as SALT-related B-cell lymphomas,⁴⁰ a term which encompasses the traditional histologic categories.

Notwithstanding these different interpretations and the debate, continued within the panel of experts of the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Study Group to establish a consensus

classification of primary cutaneous lymphomas⁵⁷, a simple and clear message should be directed at the clinician: a patient with primary CBCL has a substantial likelihood of having a localized disease that will respond well to nonaggressive treatment such as orthovolt radiotherapy. Although there is a significant risk of relapse, only a small minority of these patients will die of their disease.

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