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New aspects in the biology of cutaneous B-cell lymphomas

Immunologic and molecular genetic studies greatly contributed to a better understanding and interpretation of the distinct clinico-pathologic features of primary cutaneous B-cell lymphomas (CBCL), which are the basis for the consensus WHO-EORTC classification. There is increasingly accumulating evidence that these well defined clinico-pathologic entities of CBCL have specific immunologic and molecular features, which further support their nosologic categorization as well as either interesting similarities with other extranodal B-cell lymphomas or definite peculiarities as compared to nodal B-cell lymphomas of similar histotype (specifically, follicle center lymphoma and diffuse large B-cell lymphoma).

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The topic of primary cutaneous B-cell lymphomas (CBCL) in terms of diagnosis, classification, and historical perspective is extensively dealt with in another article of this JCP issue. As a general comment, the immunologic and molecular research in the field of CBCL considerably contributed—in addition to careful clinico-pathologic studies—to the categorization of these lymphomas first proposed in the EORTC classification¹ and recently recognized in the consensus WHO-EORTC classification.²

At present, there are many unanswered questions concerning the biology of CBCL and, more in general, of the homing of B cells into the skin and their predilection to stay localized and to proliferate in the skin 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 the Peyer's patches of the intestine or the Waldeyer's ring of the pharynx. In addition, different from T cells, B cells are not found in normal human skin. Currently, the only data concern the demonstration that sweat and sebaceous glands synthesize the secretory component of dimeric immunoglobulin (Ig)A in humans.³ Indeed, a possible speculation is that the skin and draining lymph nodes form an integrated system whereby a lymphoproliferative response to antigenic stimuli may be elicited in the

skin.⁴ In addition, it has been hypothesized 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 accumulation in the skin of lymphoid B cells. Another possibility is that a combination of etiological factors—infectious, immunologic, and genetic—may play a role in the development of lymphoproliferative B-cell disorders of the skin.

As a matter of fact, several antigenic stimuli are known to eventuate into a reactive B-cell response. These reactions, variously defined as cutaneous lymphoid hyperplasia, pseudo-B-cell lymphoma (P-CBCL), or lymphadenosis benigna cutis, may be caused by insect bites, in particular tick bites transmitting a *Borrelia burgdorferi* infection, acupuncture, antigen injections (drug eruptions, vaccinations, specific immune therapy), and tattoo pigments among others.⁵ *Borrelia burgdorferi* infection^{6–8} and tattoo pigments^{9,10} have also been suggested to be involved in the development of CBCL, in particular marginal-zone B-cell lymphomas. Interestingly, *B. burgdorferi*-specific DNA sequences have been demonstrated in a significant minority of CBCL from European areas with endemic *Borrelia* infections^{6,7} but could not be detected in CBCL from different areas in the United States¹¹ and Asia.¹² Different from *Borrelia* infection, no viral DNA sequences have been found in CBCL.¹³

Accumulating evidences suggest that these indolent CBCL (pcMZL, primary cutaneous marginal zone lymphoma; pcFCL, primary cutaneous follicle center lymphoma) and P-CBCL represent indeed a spectrum of cutaneous B-cell lymphoproliferative disorders with a step-wise progression from a reactive to a neoplastic state.^{10,14} This also explains why it can be so difficult to differentiate early stages of these indolent CBCL from P-CBCL. Apart from clinico-pathologic similarities and the above-mentioned shared association with *Borrelia* infection and tattoo pigments, clonal Ig gene rearrangements have been demonstrated not only in CBCL but also in a proportion of P-CBCL, as defined by immunohistochemical criteria.^{10,15} Interestingly, molecular analysis of CBCL recently documented intraclonal diversity with a high degree of somatic mutations, supporting the hypothesis of an antigen-driven process arising from transformed germinal-center B cells.¹⁶

Another intriguing approach to the biology of CBCL concerns the expression of chemokines (chemoattractant cytokines), especially those regulating the localization of lymphoid cells during lymphopoiesis, antigen priming, and immune surveillance, referred to as "housekeeping" (rev. in ¹⁷). In fact, it has been demonstrated that both BCA-1 (also regarded as CXCL13, the most effective B-cell chemoattractant) and CXCR5 (a chemokine receptor with predominant expression on blood and tonsillar B cells, as well as on a subset of memory CD4⁺ T-cells) are highly expressed in *Helicobacter pylori* (HP)-induced mucosa-associated lymphoid tissue (MALT) lymphoma with a distinctive pattern of expression,¹⁸ thus suggesting a possible pathogenic role of BCA-1 in the natural history of MALT lymphoma. We have recently investigated the possible involvement of BCA-1 and CXCR5 in the pathogenesis of CBCL and P-CBCL.¹⁹ First of all, no BCA-1 or CXCR5 expression was found at the immunohistochemical and molecular level in either clinically healthy skin or CTCL, thus confirming the B-cell-restricted specificity of these chemokines. The significant differences found between P-CBCL and indolent CBCL, marginal-zone lymphoma (MZL) type (CD35⁺/BCA-1⁺ dendritic cells found in lymphoid follicles of P-CBCL only; in CBCL virtually no CD35⁺ dendritic cells coexpressing BCA-1, with intensity of CXCR5 expression on CD22⁺ B cells lower than that of BCA-1),¹⁹ are in keeping with those evidenced in HP-induced MALT (gastritis) and gastric lymphoma, MALT type.¹⁸ In fact, the distribution and intensity of BCA-1 and CXCR5 in (secondary) lymphoid follicles of P-CBCL and indolent CBCL, MZL type parallel those found in HP-induced MALT (gastritis) and in gastric lymphoma, respectively. These findings add a further element to the close similarities between CBCL, MZL type, and MALT lymphoma, with

chronic antigen stimulation as a possible common pathogenic denominator.^{18,19}

There is no doubt that immunologic and molecular genetic studies greatly contributed to a better understanding and interpretation of the distinct clinico-pathologic features of CBCL, which are the basis for the EORTC¹ and the consensus WHO-EORTC classifications.² Primary cutaneous MZL (pcMZL) neoplastic cells characteristically express bcl-2 protein and are negative for bcl-6, which is a very useful additional criterion to differentiate pcMZL from primary cutaneous follicle-center lymphoma (pcFCL).^{20,21} Recent studies show the presence of the t(14;18)(q32;q21) involving the *IGH* gene on chromosome 14 and the *MLT* gene on chromosome 18 in a proportion of pcMZL.^{22,23} Other translocations observed in gastric MALT lymphomas as well as other extranodal MZL, such as t(11;18)(q21;q21) and t(1;14)(p22;q32), have not been found in pcMZL.^{23,25} pcFCL consistently express bcl-6,^{20,21,26,27} whereas they—unlike nodal and secondary cutaneous follicular lymphomas—do not express bcl-2 protein or show faint bcl-2 staining in a minority of neoplastic B cells.^{27–30} Staining for MUM-1/IRF4 is negative.^{31,32} Somatic hypermutation of variable heavy and light chain genes has been demonstrated, which further supports the follicle-center-cell origin of these lymphomas.^{16,33} In most studies, pcFCL, including cases with a follicular growth pattern, do not show the t(14;18), which is characteristically found in systemic follicular lymphomas and a proportion of systemic diffuse large B-cell lymphomas.^{29,33,34} Inactivation of p15 and p16 tumor-suppressor genes by promotor hypermethylation has been reported in a relatively small proportion of pcFCL.³⁵ In a recent study using interphase fluorescence *in situ* hybridization, no evidence for translocations involving IgH, myc, or bcl-6 loci were found.²⁵ pcFCL have the gene expression profile of germinal center-like large B-cell lymphomas.^{31,32} In contrast to the group of pcFCL, primary cutaneous large B-cell lymphoma, leg type (pcLBCL-LT) show strong bcl-2 expression, also in the much less-frequent cases not located on the legs.^{21,29,36} Different from pcFCL, most pcLBCL-LT express MUM-1/IRF4 protein.^{31,32} The t(14;18) is not found in pcLBCL, although strong bcl-2 expression is common in this group.^{29,37} In some cases, bcl-2 overexpression may result from chromosomal amplification of the *bcl-2* gene.³⁷ Inactivation of p15 and p16 tumor-suppressor genes by promotor hypermethylation has been detected in a variable proportion of pcLBCL-LT.³⁵ Chromosomal imbalances have been identified in most pcLBCL-LT, with gains in 18q and 7p and loss of 6q as most common findings.^{37–39} Recent reports showed translocations

involving *myc*, *bcl-6*, and *IgH* genes in most pcLBCL-LT but not in patients with pcFCL with a diffuse infiltration of large centrocytes.²⁵ Finally, recent studies suggest that pcLBCL-LT have an activated B-cell gene expression profile, in parallel with MUM-1/IRF4 protein expression.^{31,32}

In conclusion, there is increasingly accumulating evidence that the well defined clinico-pathologic entities of CBCL have specific immunologic and molecular features, which further support their nosologic categorization as well as either interesting similarities with other extranodal B-cell lymphomas or definite peculiarities as compared to nodal B-cell lymphomas of similar histotype (specifically, follicle center lymphoma and diffuse large B-cell lymphoma).

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