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EDITORIAL

Cutaneous B-cell lymphomas: facts and open issues

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The above case report (pp. 199–200) focuses once again on the skin as a prominent and visible site of presentation of a systemic B-cell lymphoma. This is certainly worthy of note, and pushes us to face critically the issue of B-cell non-Hodgkin's lymphomas (NHLs) and the skin.

First, primary cutaneous B-cell lymphomas (CBCLs) are an established reality, and must be clearly separated from secondary CBCLs. In fact, the former do not require aggressive treatment and their prognosis is overall excellent.[1,2] This is different from the latter, which are the expression of dissemination from a primarily extracutaneous site. It remains to be clarified whether concurrent CBCLs, i.e. those simultaneously presenting in the skin and also lymphoid organs and/or other extranodal sites (e.g. mucosa-associated lymphoid tissue, MALT) do behave different from secondary CBCLs. In our experience, the comparison of primary, concurrent and secondary CBCLs, although biased by the different size of the studied groups of patients, seems to indicate that concurrent CBCLs have clinicopathologic, immunologic and prognostic features much closer to those of primary CBCLs.[3]

The second point to be faced is how frequent is the occurrence of primary CBCLs. According to the literature and general international experience, primary CBCLs are less frequent than CTCLs, with figures varying greatly between European[2,4] and American studies.[5] However, according to the results of a population-based study carried out in the Florence district (1986–1995),[6] primary CBCLs account for 66.6% of the total number of primary cutaneous lymphoma patients ($n = 132$; the second most common extranodal NHLs, which account for more than one-third of the total number of NHLs), with a crude incidence rate of 0.7 per 100 000 inhabitants per year (standardized incidence rate = 0.5), which is clearly higher than that of CTCLs (crude incidence rate = 0.3, standardized incidence rate = 0.2). These findings can certainly be influenced by the systematic application of immunohistochemical (light chain monoclonal restriction of surface and/or cytoplasmic immunoglobulins) and molecular criteria (heavy chain monoclonal rearrangement) for the diagnosis of primary CBCLs, with the consequent higher likelihood of detecting very early cases. In this regard, a recent British study seems to confirm the more frequent and confident diagnosis of primary CBCLs as one of the major causes for the clearly increasing incidence of extranodal NHLs.[7]

Another very interesting issue, for both scientific and practical reasons, concerns the clinical relevance, the reproducibility and, more important, the prognostic significance of the categorization of primary CBCLs into specific subgroups. According to the European Organization for Research and Treatment of Cancer (EORTC) classification of primary cutaneous lymphomas,[2] primary CBCLs are divided into three subgroups. Two of them, the so-called follicle centre cell lymphoma (FCCL) and the immunocytoma/marginal zone lymphoma (MZL) due to their histological similarities with their purported nodal counterparts, account for more than 90% of all patients with a definite diagnosis of primary CBCL. They have a mostly regional extension and an indolent clinical behaviour, with good response to local radiotherapy, low tendency to extracutaneous spread, and excellent prognosis.[1,2] The main differential features are as follows. FCCLs are mainly located on the trunk and on the head and neck. Histologically, they are composed of cells reminiscent of the morphologies of FCCs, usually a mixture of small and large cleaved cells (putative centrocytes) and large cells with prominent nuclei and nucleoli (putative centroblasts and immunoblasts).[2] Additional criteria, especially in cases with a follicular growth pattern, are a reduced mantle zone, a reduced proliferation rate and the absence of tingible body macrophages in the follicle centre compared to reactive follicles, and the bcl–6+, CD10+ phenotype of neoplastic cells.[8–10] Conversely, MZLs are usually located on arms or legs. Histologically, the findings of lymphoplasmacytoid/plasmacytoid cells located at the periphery of the nodular infiltrates[2,9,11] and the 'colonization' of reactive lymphoid follicles by bcl6–, CD5–, CD10– neoplastic cells[9,11] are considered the clues to diagnosis. In our experience on a large series of 274 patients, this strict type of categorization is clinically and histologically difficult to reproduce. In fact, in the 245 patients of our series with an indolent course (89.4%), we did not observe a significant variation in the sites of presentation (trunk and head and neck vs limbs) in relation to different histology, although it was very clear that the regional extension of the disease is the rule (90.6% in our

series). Moreover, the above distinctive features of FCCLs and MZLs are very hard to find in early lesions, characterized by small clusters of centrocyte-like neoplastic B cells with a CD5–, CD10–, bcl2–, bcl6+/– phenotype and an overwhelming predominance of reactive T cells. Even in more developed lesions, different histologic pictures (FCCL-like, with CD10 antigen expression much less useful that bcl6 protein expression in our hands, and MZL-like) are often found in different lesions of the same patient (so-called 'discordant' picture) or even in different areas of the same lesion (so-called 'composite' picture). The above features plus others, including polymorphism of the neoplastic infiltrate, with cells showing a fluent transition of sizes and shapes, and variable extent of reactive T- and B-cell infiltrate according to the size, age and growth rate of skin lesions; uniformly negative bcl2 gene rearrangement;[12–14] typical, although not frequent, finding of lymphoepithelial lesions,[1] induced us to suggest the holistic interpretation of indolent primary CBCLs as skin-associated lymphoid tissue (SALT)-related B-cell lymphomas[15–17] on the basis of the close similarities with MALT lymphomas. Relative problems of categorization and subtle differences of interpretation apart, it is a fact that indolent primary CBCLs are common (nearly 90% of all primary CBCL cases), show a very good response to non-aggressive treatment (local radiotherapy), and – despite relatively frequent relapses (24.7% in our series, with a median disease-free interval of 42 months) – have an excellent prognosis (98.5% 5-year survival). One very interesting feature is the lack of correlation between histologic progression to diffuse large cell infiltrate and either the clinical course or the prognosis of the disease, which is excellent (different from nodal B-cell NHLs).[1,2] A third, much smaller, subgroup with intermediate prognosis (the so-called large B-cell lymphoma of the leg)[18] is identified in the EORTC classification.[2] It is characterized by rapid growth of skin lesions (plaques, nodules and/or tumours), *de novo* diffuse large cell infiltrate histology (diffuse large B-cell lymphoma, DLBCL), high proliferation rate, strong bcl2 protein expression, predilection for the elderly (> 70 years of age) and selected skin sites (lower legs), and much less favourable prognosis (58% 5-year survival). The results of a recently published European multicentre study on a large group of patients[19] indicate that large 'round' cell (i.e. centroblast- and immunoblast-like) histology and old age (> 70 years) are the most potent factors significantly associated with a more aggressive behaviour and worse prognosis compared to indolent primary CBCLs. Our experience with 29 patients with DLBCL (10.6% in our series of 274 patients) is in line with all the above features (old age, median 79 years, at presentation; higher relapse rate, 41.3% vs. 24.7% in the indolent group; shorter disease-free interval, 15 vs 42 months; relative predilection for the lower limbs, 17/29 patients) except for prognosis. In fact, the 5-year survival of the DLBCL group (95.1%) is not significantly different from that of the indolent group (98.5%). In addition, only one of the three patients who died of disease had lesions of the lower limbs. Our experience in this regard is shared with other groups.[14,20]

The slight differences depicted above will find, it is hoped, a reasonable explanation by further clinico-pathologic, epidemiologic and molecular studies. However, there is no doubt that primary CBCLs are a distinct entity, to be clearly separated from secondary CBCLs, and that the EORTC classification is currently the most careful and useful to categorize them.[2,4]

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