Clinicopathologic Features of Early Lesions of Cutaneous Follicular Lymphoma, Diffuse Type. Implications for Early Diagnosis and Treatment

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The new classification of primary cutaneous lymphomas published by the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC)-Cutaneous Lymphoma Task Force includes primary cutaneous follicular B-cell lymphoma (PCFCL) as a distinct entity characterized by either a follicular, diffuse, or mixed pattern of growth. Although the diffuse type of PCFCL shows histologically predominant of large cleaved cells, thus revealing similarities to the histopathologic picture of the large B-cell lymphomas, prognosis and treatment are similar to those of PCFCL variants characterized by a follicular or a mixed pattern of growth, thus underlying the need to classify all variants in one and the same group. It is yet unclear, whether cases with diffuse pattern of growth represent a morphologic “progression” of follicular cases, or if they present with a diffuse pattern of growth from the onset. We have observed in the last years several patients with PCFCL, diffuse type, and studied the clinical and histopathologic features of early lesions (flattened lesions, small papules). A clear-cut follicular pattern was always absent, and remnants of CD21+ follicular dendritic cells were present in less than half of the cases, suggesting that in most instances the growth pattern is diffuse from the beginning. Other phenotypic aspects were similar to those of the more advanced (tumor) lesions, characterized by positivity for CD20 and Bcl-6, and negativity or only focal positivity for Bcl-2 and MUM-1. In several cases we observed small papular lesions located far away (>10 cm) from the main area of involvement, demonstrating that neoplastic cells were present well beyond the clinically apparent lesion. This finding has implications on the management of these patients, as local radiotherapy does not cover the area distant from the primary tumor, thus resulting in incomplete treatment and high risk of recurrence.

Molecular Analysis of Cutaneous B-cell Lymphoma: Relevance for Diagnosis and Treatment

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Recent molecular genetic studies have contributed significantly to a better definition of the different types of cutaneous B-cell lymphomas (CBCL) and consequently to a new consensus classification for these CBCL. In this WHO-EORTC classification three main types of CBCL are distinguished: primary cutaneous marginal zone B-cell lymphoma, primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous large B-cell lymphoma, leg type (PCLBCL-LT). For many years differentiation between PCFCL with a diffuse infiltrate of large B-cells and PCLBCL-LT was controversial. Distinction between these two groups is however important because of their different prognosis (disease-related 5-year survival of 95% and 50%, respectively) and different first choice of treatment (radiotherapy versus systemic chemotherapy, respectively). Recent studies showed that these PCFCL have the gene expression profile of germinal center-like B-cell lymphomas, while PCLBCL-LT have the gene expression profile of activated B-cell type diffuse large B-cell lymphomas. Consistently, PCLBCL-LT strongly express the activated B-cell markers Mum-1/IRF-4 and FOX-P1. Array-based CGH studies and FISH analysis showed c-REL amplification in ca. 70% of PCFCL, which provides further support for their germinal center cell origin. In contrast to these PCFCL, PCLBCL-LT showed high-level amplifications of both the MAL-T1 gene and the BCL-2 gene, which may explain the strong bcl-2 protein expression in these lymphomas, as well as deletion of a small region within 9p21.3 containing the CDKN2A gene. Inactivation of CDKN2A either by deletion or by promoter hypermethylation was strongly associated with a poor prognosis, and may be used as an important adjunct in selecting appropriate treatment in patients with a PCLBCL-LT.

Evidence-Based Medicine. Skin-directed therapies are the most appropriate option for early stages disease with good prognosis. Patients with advanced disease should participate in clinical trials whereby maintenance of quality of life should be the guiding principle.
Optimizing the Systemic Treatment of CTCL
N Pimpinelli

Systemic treatment is indicated in refractory, advanced, or aggressive Cutaneous T Cell Lymphoma (CTCL). Notwithstanding no single agent, combination or sequential regimen have demonstrated a high benefit/risk profile and considering that some drugs are not yet available in Europe, the scenario has substantially changed in the last few years according to many clinical studies (most of them non-randomized and non-controlled). Oral bexarotene is a valid alternative option both in stage I-IIA mycosis fungoides (MF) patients refractory (or plurilapsed after) skin-directed treatments and in advanced stage (IIB-IV) MF and Sezary syndrome (SS) patients refractory to or relapsing after a first line of systemic treatment. The role of bexarotene in patients in CR/PR/SD after a first line of systemic treatment is currently under evaluation. Monochemotherapy (gemcitabine, pegylated liposomal doxorubicin) is a valuable first line therapeutic option for patients with stage IIB and stage III MF or SS, as an alternative to radiotherapy (TSEBi +/- superficial radiotherapy), PUVA/FN, and extracorporeal photochemotherapy, respectively. Alemtuzumab is a further, alternative or sequential option for stage III MF and SS patients. As a rule, polychemotherapy is not recommended for first-line treatment of stage IIB-III MF, due to lacking advantages in terms of DFS and OS, the high risk of immunosuppression, and the relevant reduction in quality of life. Patients who are refractory to or relapsing after at least two lines of systemic treatment should be considered for high-dose chemotherapy and stem cell transplantation.