Complex pathological diagnosis of follicular lymphomas
Erika Toth PhD Dissertation Summary

Follicular lymphoma (FL) is the most common subtype of indolent lymphoma. Follicular lymphoma is a neoplasm associated with follicle centre B cells. Approximately 85–90% of FLs carry the t(14;18)(q32;q21) chromosomal translocation, juxtaposing the BCL-2 gene with the immunoglobulin (Ig) heavy chain (H) gene, resulting in the constitutive expression of bcl-2 protein.

Our aim was to survey and revise FLs had been diagnosed from 1990 to 1995 in the National Institute of Oncology. We studied the diagnostic relevance of histology, immunohistochemistry and the detection of immunoglobulin heavy chain (IgH) and bcl-2 gene rearrangements in 53 cases that were diagnosed as follicular, centrocytic, or mixed centrocytic-centroblastic lymphoma previously. Our aim was also to develop a new real-time polymerase chain reaction assay applicable for simultaneous quantification and characterization of the specific MBR/JH fusion in FLs and to provide further insight into the pathways of BM involvement of follicular lymphoma, we performed morphological, immunophenotypical analysis and mutational analysis of the IgVH genes on FL samples originating from LNs and BMs.

Our results underline that the main diagnostic criteria of follicular lymphomas are: 1. Loss of polarization of germinal centers (GCs). No light and dark zone and tingible body macrophages. Typical asymmetric mantle zone is not present. 2. Bcl-2 protein overexpression in GCs; 3. Proliferation rate is reduced; 4. Interfollicular infiltration of CD10 and bcl-6 positive tumour cells; 5. Bcl-2 gene rearrangement; 6. Presence of partially nodular FDC (follicular dendritic cell) meshwork. Our findings also underline the importance of determining the clonal identity between the tumour and residual cells during detection of minimal residual disease. It is crucial to avoid unnecessary treatment of patients. On the basis of our results we suggest the use of the FRET-labelled probe and primer combined with SYBR Green I fluorescent melting curve analysis. This is a fast, easy and cost-effective method for quantification and characterization of the BCL2 gene rearrangement and can improve the management of patients with FL. Our results show that the cytological grade, immunophenotype and mutation pattern of IgVH genes of FL cells are frequently different in the lymph nodes (LNs) and the matching bone marrows (BM). Our results also provide evidence that the BM provides a microenvironment similar to that of LNs, where tumour cells retain the ongoing nature of the mutations of their IgVH genes, and mutations accumulate in a way suggesting that tumour cells have been selected by antigen. The results of the present analysis provide evidence that the BM infiltration of FL is composed of a heterogeneous tumour cell population. Since the majority of BM and LN clones are derivatives of a common unidentified progenitor, it is possible that pre-neoplastic/ neoplastic B-cells migrate to the LN and the BM, and some of the tumour clones may evolve independently from each other at the two sites. The LN-independent growth of BM tumour clones is also supported by the presence of FDC in the BM, which provide a microenvironment necessary for the survival of tumour cells. All together, our findings provide evidence that the BM involvement of FL is associated with intensive clonal selection of tumour cells.