TO THE EDITOR:

The recently published proposal for a revised European-American Classification of lymphoid neoplasms (REAL Classification) by an international group of expert hematopathologists is an admirable assay to reach consensus in lymphoma classification. As the authors say, they tried to define real disease entities using currently available morphologic, immunologic, and genetic techniques.

In fact, what resulted was the recognition of a mixture of lymphomas originally already defined in earlier classifications, some newly defined or named entities and quite a number of provisional entities of which it is by no means certain that they are clinicopathologic entities.

We agree with the authors that delineation of clinicopathologic entities with well-defined histologic and clinical features, including a predictable clinical course, response to therapy and prognosis, should be the ultimate goal of any lymphoma classification. However, we do not believe that this goal can be reached on the basis of histologic, immunologic, and genetic criteria alone. Recent studies have shown convincingly that morphologically identical lymphomas arising at different sites may have a completely different clinical behavior and prognosis. For instance, anaplastic large cell lymphomas arising in the skin have a favorable prognosis, as compared with anaplastic large cell lymphomas originating in lymph nodes. On the other hand, anaplastic large cell lymphomas of the intestinal tract have a very poor prognosis, worse than nodal lymphomas. Similarly, immunocytomas and follicular center cell lymphomas originating in the skin have a much better prognosis than immunocytomas and follicular center cell lymphomas originating in lymph nodes. This implicates that many terms used in this revised European-American classification are still primarily histologic terms, and can not be considered as clinicopathologic entities. They do not give the clinician any information on the clinical course and prognosis unless the site of origin is provided as well.

There is increasing evidence that these morphologically identical lymphomas arising at different sites may not only differ in clinical behavior, but may also show differences in the expression of oncoproteins, adhesion molecules, and certain DNA/RNA viral sequences. These studies indicate differences in lymphomagenesis and/or the regulation of tumor cell growth, and strongly suggest that these lymphomas with a similar morphology, but arising at different sites should be considered as distinct biologic entities.

Recent studies on the mechanisms of lymphocyte recirculation, showing that lymphocytes have organ-specific homing patterns, have provided a theoretical basis for the differences in clinical behavior between morphologically identical lymphomas arising at different sites. Thus, lymphocytes originating in the peripheral lymph nodes home preferentially to the peripheral lymph nodes and lymphocytes originating in the mucosa-associated lymphoid tissue home preferentially to Peyer’s plaques and mesenteric lymph nodes. This tissue specific recirculation of lymphocytes is regulated by interaction of organ-specific adhesion receptors and their ligands on high endothelial venules called vascular adrenergic or tissue position markers. Thus, L-selectin is found on node-seeking lymphocytes, eC3β7 on mucosa-seeking lymphocytes, and the cutaneous lymphocyte antigen on skin-seeking T lymphocytes. There is increasing evidence that the neoplastic cells of lymphomas at those sites also express these specific lymphocyte homing receptors. Although the exact molecular mechanisms of tissue-specific recirculation are not completely understood, these observations provide a firm basis to adapt the concept of non-Hodgkin’s lymphoma (NHL). Thus, NHL can now be defined as neoplastic equivalents of recirculating functional subsets of tissue-restricted lymphocytes after antigenic stimulation. This concept stresses primary site as a potential additional important prognostic factor. Therefore, in future classification schemes malignant lymphomas should first be classified according to site. This fact was already recognized by Lennert et al when they proposed the updated Kiel classification especially for NHL originating in the lymph node. A proposal for such a classification for the group of primary cutaneous lymphomas has been published recently.

By this approach one is more likely to define real clinicopathologic entities, and to arrive at a clinically relevant classification. Although the authors of the revised European-American classification recognize some specific types of extranodal lymphomas, the concept of tissue-restricted malignant lymphomas was largely omitted. Not taking into account that morphologically identical lymphomas arising at different sites may have a completely different prognosis, severely limits the clinical relevance of this REAL classification. It also implies, in our view, that the opportunity for a REAL breakthrough in the classification of NHLs has been missed.

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