

Comment on Willemze et al, page 3768

Latest lymphoma classification is skin deep

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Cutaneous lymphomas have a distinct natural history that requires a separate classification system, as put forward by Willemze and colleagues in this issue of *Blood*.

Primarily cutaneous lymphomas are the second most common type of extranodal lymphoma (after gastrointestinal lymphomas). They require specific recognition because of their distinctive biology and clinical behavior. The prognosis for cutaneous lymphomas as a group is more favorable than for nodal lymphomas. For example, primary cutaneous anaplastic large-cell lymphomas (ALCLs) have an excellent prognosis and usually lack the anaplastic large-cell lymphoma kinase (ALK) responsible for the pathogenesis of the more aggressive ALCL of nodal origin.¹ Most follicular lymphomas of nodal origin contain rearrangements of *BCL-2* oncogene and present as widespread stage III or IV disease, whereas primary cutaneous follicular lymphomas usually lack *BCL-2* gene rearrangements and are often localized to the scalp, forehead, or trunk² (see Figure 9 in the

article by Willemze and colleagues). Distinction of primary cutaneous lymphomas from secondary skin lesions in systemic lymphomas can be difficult and requires careful correlation of clinical, pathologic, immunologic, and genetic data. This information is provided in the new World Health Organization–European Organization for Research and Treatment of Cancer (WHO–EORTC) classification formulated by Willemze and colleagues.

Lymphoma classifications evolve as our knowledge of biology improves. An earlier EORTC classification of primary cutaneous lymphomas was published in *Blood* less than 10 years ago,³ followed by a WHO classification of tumors of hematopoietic and lymphoid origin.⁴ The current WHO–EORTC classification reconciles differences in terminology between these 2 sources and updates our understanding of differences in the biology of

cutaneous and systemic lymphomas. Importantly, the new classification system is validated by clinical follow-up data on 1905 patients from the Dutch and Austrian Cutaneous registries for primary cutaneous lymphomas.

The WHO–EORTC classification is a useful guide for the practicing hematologist–oncologist who is consulted for management of cutaneous lymphomas, more often in the United States than in Europe, where such patients may be cared for primarily by dermatologists. The WHO–EORTC classification groups together cutaneous lymphomas of T-cell or B-cell origin. Other rare cutaneous lymphomas originate from natural killer cells or CD4⁺/CD56⁺ plasmacytoid dendritic cells of bone marrow origin. More than 90% of cutaneous lymphomas can be accounted for by the lymphomas listed in the table. The diffuse large B-cell lymphoma, usually arising in the leg of elderly women, is a unique cutaneous lymphoma. The absence of mantle zone lymphomas and rarity of Hodgkin disease in the skin emphasize the difference between cutaneous and systemic lymphomas.

Is there room for improvement in the current classification scheme? I believe so. Future versions should include specific delineation of morphologic variants that may be difficult to recognize as lymphoma, such as the “neutrophil-rich” variant of ALCL that can be confused with a nonmalignant inflammatory process; in this variant relatively few lymphoma cells may be overlooked in a sea of neutrophils but are revealed with a stain for CD30 antigen.⁵ Also worthy of inclusion is primary cutaneous lymphoma of precursor B-lymphoblastic origin, which usually presents in children and young adults.⁶ Future versions would likely benefit from participation of clinicians from countries outside of Europe. Nevertheless, the current document represents a significant advance in the classification of cutaneous lymphomas that should be within reach of clinicians and pathologists involved in the care of patients with cutaneous lymphomas. ■

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| Lymphoma type | Fr |
|---|-----|
| Mycosis fungoides and its follicular tropic variant | 48% |
| Sézary syndrome | 3% |
| Anaplastic large-cell lymphoma | 8% |
| Lymphomatoid papulosis | 12% |
| Follicular center lymphoma | 11% |
| Marginal zone B-cell lymphoma | 7% |
| Diffuse large B-cell lymphoma, leg type | 4% |
| Total | 93% |

The most common primary cutaneous lymphomas. The large majority (93%) of cutaneous lymphoma cases are manifestations of the relatively small number of types listed in this table; while many other types of lymphoma are discussed by Willemze and colleagues, they comprise just 7% of cutaneous lymphoma cases. Fr indicates frequency.