The primary cutaneous CD30-positive (CD30+) T-cell lymphoproliferative disorders are a group of largely indolent diseases that manifest as nodules or tumors of the skin. The European Organisation for Research and Treatment of Cancer (EORTC) has developed a modification of the World Health Organization (WHO) lymphoma classification system that specifically categorizes these entities.

According to Willemze et al, the CD30+ diseases include primary anaplastic large-cell lymphoma (ALCL), primary CD30+ lymphoproliferative disorder, and lymphomatoid papulosis (LyP).[1] Collectively, these are a common type of cutaneous T-cell lymphomas (CTCL), comprising 25% of cases. Often confused with more aggressive T-cell lymphomas with similar histopathologic features, these diseases are difficult to diagnose and poorly understood. The differential diagnosis of CD30+ CTCL includes the CD30+ lymphoproliferative disorders (primary cutaneous ALCL, LyP), secondary cutaneous lymphomas (systemic ALCL, systemic CD30+ peripheral T-cell lymphoma), CD30+ mycosis fungoides variants, and reactive skin conditions (arthropod bites, scabies, drug eruptions, atopic dermatitis, and viral infections).

**Disease Spectrum**

Kadin details the spectrum of these disorders, focusing on the benign nature of most subtypes. It is important to distinguish the benign from the potentially malignant or progressive entities. While LyP and primary ALCL of the skin appear as nodular lesions or tumors and have similar histopathologic features, with large anaplastic CD30+ cells infiltrating the dermis, the distinction between the two is related to depth of invasion of the infiltrate as well as to the clinical features and evolution of the disease in the patient. LyP is considered to be largely an indolent disorder, with spontaneously healing skin papules and nodules occurring often over years; primary cutaneous ALCL may be indistinguishable from its more aggressive systemic counterpart but it remains an indolent process with spontaneous regression in 25% of cases.

With overlapping clinical and histopathologic features, how does the clinician distinguish what is most likely a primary cutaneous ALCL or LyP from cutaneous manifestations of systemic ALCL? Kadin describes immunohistochemical studies, including expression of epithelial membrane antigen and cutaneous lymphocytes antigen, which distinguish systemic ALCL from the more indolent cutaneous entities. Likewise, other skin disorders, specifically pityriasis lichenoides et varioliformis acuta (PLEVA), can be confused with CD30+ disorders of the skin, with differences being the presence of CD30+ cells and CD4+ lymphocytes in the infiltrates of LyP and primary cutaneous ALCL, whereas PLEVA infiltrates demonstrate predominantly CD8+ lymphocytes.

**Staging and Risk of Malignancy**

Appropriate staging for all newly diagnosed patients with CD30+ primary cutaneous lymphoproliferative disease (PCLPD) includes imaging studies of lymph nodes and visceral sites to rule out systemic involvement. The role of bone marrow biopsy is less well delineated. Bone marrow is rarely involved in patients with PCLPD and may be deferred except in patients who demonstrate evidence of extracutaneous involvement. Careful staging is paramount in all patients in order to determine whether systemic therapy is appropriate and to spare patients with primary cutaneous disease from unnecessary exposure to aggressive systemic chemotherapy.

The risk of progression of LyP and PCLPD to systemic malignant lymphoma is of concern for both
clinicians and patients with PCLPD. While patients with PLEVA have no risk of associated malignancy, the risk is increased in patients with PCLPD. In a prior retrospective review of 118 patients from the Netherlands, 19% of patients with LyP developed a systemic lymphoma, including mycosis fungoides (n = 11), Hodgkin disease (n = 2), and systemic CD30+ lymphomas (n = 10).[2] Of the 118 patients with LyP, 96% were alive at 10 years. In Kadin’s case-control study of 57 LyP patients, 28% developed lymphomas. Kadin also describes an increased risk of nonlymphoid malignancies compared with controls in these patients, with a relative risk of 3.11 compared to the Surveillance, Epidemiology, and End Results (SEER) database. These results dictate that careful follow-up of patients is warranted.

**Individualized Treatment**

Treatment for the CD30+ cutaneous disorders is individualized based on patient disease characteristics and often involves careful follow-up without aggressive interventions. For patients with recurring LyP, a number of therapies have been used, including light-based therapies (psoralen plus ultraviolet A or ultraviolet B [PUVA/UVB]), oral methotrexate, interferons, and topical or systemic retinoids. Methotrexate has been the mainstay of therapy for most patients as it is effective and well-tolerated. For patients with CD30+ cutaneous ALCL with a solitary or small number of localized lesions, radiation therapy can be curative. For relapsed patients or those with more disseminated involvement, single-agent chemotherapy with such drugs as methotrexate or etoposide is effective. Most recently, anti-CD30+ antibodies have been shown to induce remissions in patients with relapsed cutaneous ALCL.

**Conclusion**

In summary, Kadin’s article provides an excellent summary and a guide for management of these difficult disorders. For medical oncologists who may not see a wide spectrum of patients with these disorders, careful staging and accurate characterization of patients into those with systemic disease and those with cutaneous disease only is paramount to treatment planning and management. As pointed out by Kadin, a multidisciplinary approach with dermatology, radiation oncology, and medical oncology is preferred for most patients.

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