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Cutaneous CD30 lymphoproliferative disorders and similar conditions: a clinical and pathologic prospective on a complex issue

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We elaborate on the diagnosis of CD30 positive cutaneous lymphoproliferative conditions including the various clinical and pathological presentations, our understanding of its pathomechanisms and prognostic implications. The most common reactive conditions that can simulate CD30 lymphoproliferative conditions, including arthropod bite reactions, various viral infections, pityriasis lichenoides and lymphocytic papules in myelodysplastic syndrome, are discussed in detail.

The World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) consensus classification of cutaneous lymphomas recognizes a distinct g5roup of primary cutaneous CD30-positive lymphoproliferative diseases ($CD30^+$ LPD) that represent the second most common types of cutaneous T-cell lymphomas (CTCL) accounting for approximately 30% of all CTCL.[1,2] The spectrum of $CD30^+$ LPD includes lymphomatoid papulosis (LyP), cutaneous anaplastic large cell lymphoma (CALCL), and borderline cases. The inclusion of this category in the classification of cutaneous lymphomas is controversial. Especially because CD30 is not always expressed in the so-called $CD30^+$ LPD and, in addition, numerous other skin conditions, including inflammatory reactions and other lymphoproliferative disorders, may also express CD30. Furthermore, LyP by definition is a waxing and waning process that resolves spontaneously, hence its inclusion in the lymphoma classification is misleading. In this article, we will review our present understanding of $CD30^+$ LPD with a critical assessment of its nature and elaborate on reactive conditions that can resemble them.

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Lymphomatoid papulosis

LyP was first described in 1971 by Macaulay to characterize a chronic self-healing and recurrent condition composed of erythematous papules and nodules on trunk and extremities that often occur in clusters or present as many disseminated lesions.[3] The number of lesions is highly variable from patient to patient. They tend to become necrotic and hemorrhagic with eventual spontaneous regression often resolving with discrete pox-like scars (Figure 1). In general, the process lasts 3-12 weeks, although in some severe cases or cases localized to one anatomic region, the lesions may be more durable. One could consider the diagnosis of papular mycosis fungoides (MF) for these presentations. However, we have observed the typical pathology of LyP in patients with this localized or regional presentation. Unusual presentations include a large plaque variant composed of ag-

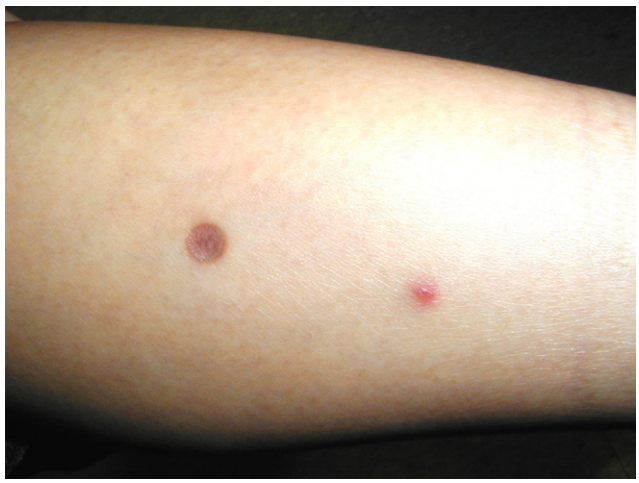

Figure 1 Early erythematous lymphomatoid papulosis lesion (right) with adjacent pox-like scar of a resolved lesion (left).

minated and more persistent papules,[4] a follicular-based variant, a more inflammatory or vesicular, and pustular presentation and cases with the clinical appearance of exophytic eroded nodules resembling pyogenic granuloma with the pathologic correlate of pseudoepitheliomatous hyperplasia as well as neutrophilic infiltrate and atypical large lymphocytes.[5] Genital and oral mucosal involvement has been rarely observed.[6] Another curious presentation is regional LyP were the lesions are localized to one anatomical area, usually involving an extremity.[7] We have observed a nodal lymphoma in the draining nodal basin area. These regional presentations as well as the also localized agminated cases reported by Heald may suggest a local cytokine environment that favors tumor growth. Nodal lymphomas in the draining basin have been reported.[8] One could hypothesize that some of these regional lesions involving the draining limb and resembling LyP may be secondary to retrograde lymphatic obstruction from a primary nodal lymphoma. The course of LyP is highly variable. The condition can eventually and permanently resolve or persist for decades. In some patients, the lesions persist chronically in a dynamic waxing and waning fashion, whereas others have outbreaks of lesions that may be unpredictable, seasonal, or triggered by stress, illnesses, or a variety of other claims.

LyP, previously considered as a benign inflammatory process within the spectrum of pityriasis lichenoides, is now regarded as an indolent cutaneous lymphoproliferative disorder. The association with a second malignant lymphoma varies depending on the series but is probably in between 10% and 20% of cases. The most common associated lymphoma is MF and rarely systemic lymphomas.

Histologic features depend largely on the timing of the biopsy and the phase of the specific lesion evolution. A typical lesion of LyP will show a wedge-shaped pattern of a dermal lymphocytic infiltrate. Generally, three histologic types have been identified, characterized as types A, B, and C, which may present with overlapping features. LyP, type A or "histiocytic type" and type C with the same cytomorphology, consist of large atypical lymphocytes resembling Reed–Sternberg cells. Type A cells are embedded in a dense inflammatory background with histiocytes, small lymphocytes, neutrophils, and eosinophils, and can resemble Hodgkin's disease, whereas type C is characterized by sheets of similar large atypical lymphocytes with prominent lavender nucleoli, open chromatin, and abundant pale cytoplasm with fewer interspersed inflammatory cells (Figure 2A-D). The main distinction between type A and type C is seen clinically with the small papular nature of type A versus the large long-lasting nodular or tumoral lesions more typical of type C. Type B simulates classical MF with epidermotropism and a dermal band-like infiltrate composed of small- to medium-sized hyperconvoluted T cells. The distinction between type B LyP and MF cannot be made by histology or immunophenotyping because both can have the same features. The diagnosis depends on the clinical presentation. To further confuse the issue, a papular variant of MF has been recently reported.[9] Furthermore, incipient lesions of type A LyP may have a similar appearance as type B, and coexistence of type A and type B lesions has been simultaneously reported in the same patient.[10]

The atypical lymphoid cells typically exhibit a $CD4^+$ $CD8^-$ $CD30^+$ T-helper phenotype and frequently express cytotoxic proteins such as TIA-1 and less commonly granzyme B and perforin.[11] Occasionally, LyP has a $CD8^+$ or $CD4^-/CD8^-$ null phenotype. A higher incidence of CD8-predominant cases has been found in pediatric patients.[12] Pan-T-cell markers, such as CD2, CD3, and CD5, are usually expressed, but CD7 is frequently absent. The expression of CD15, a marker for Hodgkin lymphoma and Reed–Sternberg cells, has been reported, but staining for CD15 is generally negative and, when present, the diagnosis of metastatic Hodgkin's disease should be considered.[13] However, recent study showed CD15 expression in 18% of LyP cases compared with 43% of CALCL.[14]

The anaplastic lymphoma kinase protein (ALK-1) is usually negative and coexpression of CD56 is observed in rare cases, but does not appear to be associated with an unfavorable prognosis.[15] Pseudocarcinomatous epidermal hyperplasia was found in cases of LyP and $CD30^+$ CALCL possibly associated with epidermal growth factor dysregulation.[38] In our experience, most of these cases with prominent pseudoepitheliomatous hyperplasia are also characterized by a dense neutrophilic infiltrate (Figure 3). The expression of ALK-1 or epithelial membrane antigen (EMA) by the tumor cells may indicate a skin tumor secondary to a systemic lymphoma. Recently, published immunohistochemical data suggest that markers, such as fascin, survivin, bcl2, CD134, and TRAF1, may help distinguish LyP from similar appearing cutaneous metastasis of nodal anaplastic lymphomas.[17,18] However, we are very skeptical about markers that claim prognostic value, and in our opinion, a reliable marker has yet to be identified. In support of our concept, a recent study suggests that phenotypic expression of TRAF1, MUM1, bcl-2, and CD15 can-