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A new era for cutaneous CD30-positive T-cell lymphoproliferative disorders

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ABSTRACT

Cutaneous CD30+ T-cell lymphoproliferative disorders (CD30+ T-LPD) represent a spectrum encompassing lymphomatoid papulosis (LyP), primary cutaneous anaplastic large-cell lymphoma (pcALCL) and borderline lesions. They share the expression of CD30 as a common phenotypic marker. They differ however in their clinical presentation, the histological features and clinical course. Moreover, LyP and PcALCL show numerous clinical, histological and phenotypic variants. Overlapping features of LyP and pcALCL with themselves and with other cutaneous and systemic lymphomas emphasize the importance of careful clinicopathologic correlation and staging in the diagnosis of CD30+ T-LPD. Furthermore, an increasing number of inflammatory and infectious skin disorders harboring medium-sized to large CD30+ cells have to be considered in the differential diagnosis.

Whereas the expression of CD30 in cutaneous CD30+ T-LPD stands for a favourable prognosis, its expression in other cutaneous and systemic lymphomas has a divergent impact. The assessment of CD30 expression does not only provide prognostic information, but is of potential therapeutic relevance as CD30 can serve as a therapeutic target.

This review focuses on the clinicopathological and phenotypic spectrum of CD30+ T-LPD, its differential diagnoses and the role of CD30 as a diagnostic, prognostic and therapeutic marker.

Overview

Primary cutaneous CD30+ T-cell lymphoproliferative disorders (CD30+ T-LPD) are the second most common form of cutaneous T-cell lymphomas (CTCL) and account for approximately 30% of all primary cutaneous lymphomas (CL).[1,2] CD30+ T-LPD represent a spectrum of disorders, which include lymphomatoid papulosis (LyP), primary cutaneous anaplastic large-cell lymphoma (pcALCL) and borderline lesions. Their common immunophenotypic hallmark is the expression of CD30 by atypical T-lymphocytes. CD30, which was discovered in 1982 by Stein and coworkers and initially referred to as Ki-1, is a cytokine receptor belonging to the tumor necrosis factor receptor (TNFR) superfamily.[3] It is involved in the growth control of CD30+ tumor cells with divergent effects on apoptosis and proliferation in cutaneous CD30+ T-LPD and systemic CD30+ lymphomas.[4,5]

LyP and pcALCL show overlapping morphological and immunophenotypic features, but they significantly differ in their clinical presentation. In addition, CD30+ T-LPD may show overlapping or even identical histological and immunophenotypic features with secondary cutaneous involvement by Hodgkin lymphoma (HL) and systemic ALCL. This implies that careful clinicopathologic correlation and staging examination are mandatory for the diagnostic work-up of cutaneous infiltrates of atypical CD30+ lymphocytes.[6,7]

Both LyP and pcALCL show a wide spectrum of clinical, histological and immunophenotypic variants. Moreover, expression of CD30 can be observed to a variable degree in other cutaneous T-and B-cell lymphomas and in systemic lymphomas such as adult T-cell leukemia/lymphoma and extranodal NK/T-cell lymphoma, nasal type. Furthermore, the presence of atypical CD30+ cells is not restricted to lymphomas, since various inflammatory and infectious disorders can harbor CD30+ medium-sized to large atypically appearing T-cells, as seen in arthropod bite reactions, thereby simulating CD30+ T-LPD.[8,9]

In contrast to systemic ALCL and HL, cutaneous CD30+ T-LPD exhibit a favourable prognosis.[6] As a consequence, the management of CD30+ T-LPD differs from the treatment modalities employed in systemic CD30+ lymphomas.[7] To emphasize these biologic differences between primary cutaneous and systemic CD30+ lymphomas, cutaneous CD30+ T-LPD are listed as distinct nosologic entities in the WHO classification (4th edition, 2008 and updated 4th edition, 2016).[10,11]

CD30 is not only an important diagnostic and prognostic marker. Recently, it has become a therapeutic target for antibody-

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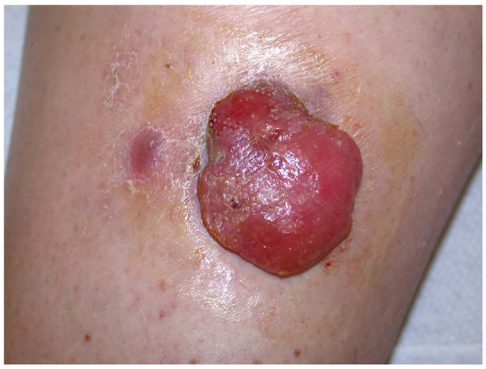

Fig. 1. Primary cutaneous anaplastic large-cell lymphoma: poylpoid and eroded tumor on the leg. *Note*: smaller tumoral lesion in the surrounding skin.

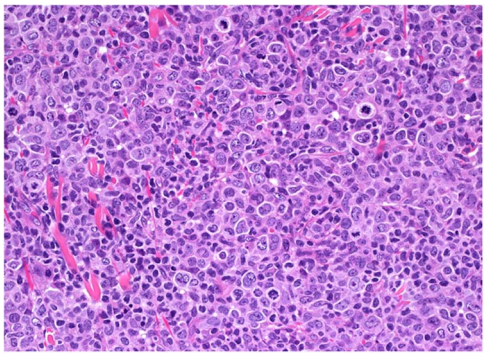

Fig. 2. Primary cutaneous anaplastic large-cell lymphoma: dense cohesive infiltrates of large pleomorphic and anaplastic lymphoid cells (H&E, magnification ×200).

based therapy. The unique features of cutaneous CD30+ T-LPD, especially the discrepancy between the cytomorphology of the tumor cells suggesting high-grade malignancy and the paradoxical biological behaviour with a favourable prognosis, and the spontaneous regression of lesions in LyP make cutaneous CD30+ T-LPD an interesting model disease for lymphomagenesis.

This review describes the clinicopathologic features of CD30+ T-LPD, thereby focusing on recently identified new variants, their differential diagnoses, the impact of clinico-pathological correlation for the diagnosis, and the role of CD30 as a diagnostic, prognostic and therapeutic marker in cutaneous lymphomas and non-lymphoid neoplasms.

Primary cutaneous anaplastic large-cell lymphoma.

Introduction

By definition, pcALCL is characterized by large T-cells with prominent nuclear pleomorphism and expression of CD30 by more than 75% of tumor cells.[1,2,10] PcALCL was delineated as a distinct form of ALCL, since the course of pcALCL significantly differs from the systemic forms ALCL, both ALK-positive and ALK-negative.[12] In addition, phenotypic and genetic studies showed major differences between pcALCL and sALCL.[5,13] Unexpectedly, the highly atypical cytomorphology of the CD30+ tumor cells and the rapid growth of tumoral lesions contrast with the favorable prognosis of pcALCL.

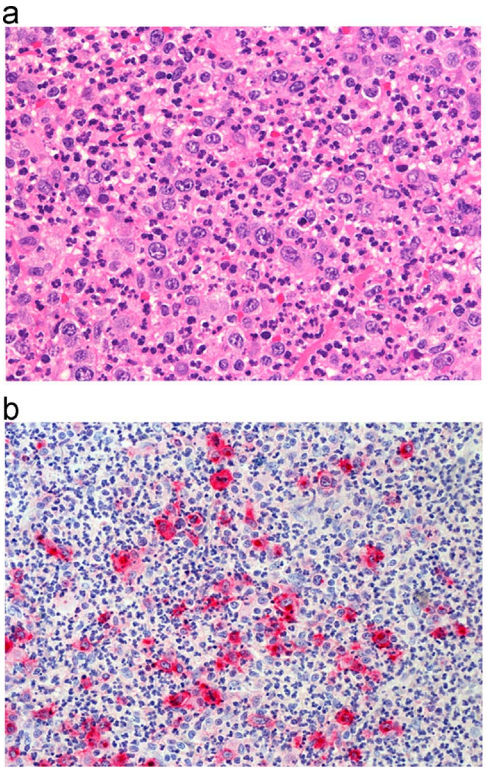

Fig. 3. Primary cutaneous anaplastic large-cell lymphoma, neutrophil-rich variant: scattered anaplastic tumor cells in the background of numerous neutrophils (A; H&E, magnification ×200). CD30 stain highlights the tumor cells (B; IHC, CD30 stain, magnification ×200).

Clinical features

PcALCL mainly affects people in their sixth decade with a male to female ratio of 2–3: 1, but it can also occur in childhood .[5,6,13] PcALCL is a common form of cutaneous T-cell lymphoma in HIV-infected individuals and organ transplant recipients.[14,15] It manifests in most patients with a solitary tumor or grouped nodules of firm consistency, which show rapid tumor growth. The tumors may reach a size of several centimeters and often show ulceration (Fig. 1). Approximately 20% of the patients have multifocal disease with 2 or more lesions at different anatomic sites.[6,16] The head and neck area as well as the extremities represent predilection sites for pcALCL.[5] Remarkably, spontaneous tumor regression is reported to occur in 10–42% of tumoral lesions in pcALCL.[6,7] In the author's experience recurrences after spontaneous regression, however, are common and complete remission without therapeutic intervention is exceptional. Recent reports indicate that pcALCL may be induced by immunomodulating drugs such as adalimumab and fingolimid.[17,18]

Microscopic features

The archetypic histological feature of pcALCL is a circumscribed nodular infiltrate of cohesively arranged large lymphoid cells extending into the deep dermis or subcutis. The tumor cells show a pleomorphic, anaplastic or an immunoblastic morphology with round, irregularly shaped nuclei and one or more nucleoli, and abundant pale cytoplasm (Fig. 2). In most cases, only a few neutrophils or eosinophils are present. Epidermotropism is usually absent or subtle. Ulceration may be present. Neutrophil-rich and eosinophil-rich forms of the disease, however, have been described and appear to be more common in immunodeficient

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