Primary Cutaneous Lymphomas/Lymphoproliferative Disorders with T Follicular Helper Phenotype: A Tertiary Cancer Center Experience

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INTRODUCTION: Primary cutaneous lymphocytic proliferations showing T follicular helper (TFH) phenotype comprise CD4+ small medium T cell lymphoproliferative disorder (CD4+SMLPD) and rare examples of mycosis fungoides (MF)/ Sézary syndrome (SS) and CD30+ T cell LPD. Systemic TFH lymphomas such as angioimmunoblastic T cell lymphoma (AITL) may also involve the skin. However, primary cutaneous lesions showing TFH phenotype and lacking the typical clinicopathological features of CD4+SMLPD, MF, or AITL are rarely encountered. Learning objective is to characterize clinical and histopathologic features of a large cohort of primary cutaneous lymphoma/LPD with TFH phenotype.

METHODS: Retrospective and prospective study of patients with diagnosis of cutaneous T-cell lymphoma/LPD with TFH phenotype seen in the last 20 years, confirmed with the expression of at least two of the following TFH markers: PD-1, CXCL13, ICOS, BCL6, and CD10. Exclusion criteria included a known history of typical patch/plaque mycosis fungoides and evidence of systemic/nodal lymphoma at the time or before the cutaneous presentations. Clinical and histopathological features studied.

RESULTS: 65 skin biopsies from 15 patients (pts) were studied consisting of 7 men and 8 women (median age: 64 [19-80 y]), with 32 months of median follow-up. Cutaneous presentations varied from mostly multiple pink-erythematous urticarial patches, papules/plaques (10 pts); to violaceous indurated papules, nodules and/or plaques (4 pts); ulceration (3 pts) and erythroderma (1 pt). The lesions were distributed on the trunk, extremities, as well as face and scalp (80%, 60%, and 30%, respectively). Seven patients had stable disease or regression of the lesions, while 8 progressed with lymph node (LN) and/or bone marrow (BM) involvement. Three patients died of disease (median overall survival: 33 months). History of immune dysregulation was noted in 5 patients (autoimmune disease and prior immunotherapy for cancer). Histopathological findings included mostly a dermal infiltrate (diffuse, nodular to perivascular and periadnexal) of small to medium-sized atypical lymphocytes with scattered large cells with frequent admixture of B-cells, histiocytes, plasma cells, and eosinophils. The T-cell infiltrate was CD4-positive (15/15) and showed predominance of CD4 over CD8 expression with the CD4:CD8 ratio ranging from 3:1 to 8:1; partial loss of CD7 (14/15); with expression of at least two TFH markers; occasional CD30 positivity and lack of Epstein-Barr virus association. Clonal TCR rearrangements were detected (14/15). Next gene sequencing performed in 5 patients identified *TET2, DMNT3A, BCL10, ITPKB* and *PLCG* mutations. Further analysis found specimens from patients who progressed into systemic disease with LN and/or BM involvement less likely to have epidermotropism (7 out of 8, p-value 0.07).

CONCLUSION: Primary cutaneous TFH lymphomas/LPD may constitute a separate group of diseases with clinical presentations not typical of MF/SS, CD4+SMLPD, or TFH lymphomas included in the current World Health Organization classification (fifth edition, 2022) and showing a spectrum of outcomes. Dermatopathologists and clinicians need to be aware of this entity as the recognition of TFH phenotype in these processes can be important for diagnosis, follow up, and potential benefit from targeted therapies.