CLA and TRAF-1 are Useful in Differentiating Lymphomatoid Papulosis, Cutaneous ALCL and Systemic ALCL.

Hernani Cualing, MD,1,2,3 E. Kadin, MD,2,4,5 Frank Glass, MD,2
Department of Pathology
The University of South Florida College of Medicine,2,3 Tampa, FL and Roger Williams Medical Center2, Providence RI

ABSTRACT
Cutaneous T cell lymphomas and the CD30+ group of T-cell lymphoproliferative disorders are relatively rare and present diagnostic challenges. Lymphomatoid papulosis (LyP), primary cutaneous anaplastic large T-cell lymphoma (pcALCL) and cutaneous inﬁltrates of systemic anaplastic large T-cell lymphoma (sALCL) are CD30+ positive lymphoproliferative disorders of the skin that overlap clinically, histopathologically, and immunophenotypically, but differ in prognosis. In particular, lesions of LyP regress spontaneously, whereas those of pcALCL persist and may spread to extracutaneous sites. Secondary skin lesions confer a poor prognosis in sALCL. In this study we show that differential expression of novel biomarkers may reliably distinguish LyP primary cutaneous ALCL, from systemic ALCL. We used antibodies against TRAF-1 (Tumor Necrosis Receptor Associated Factor 1) (Cutaneous Lymphocyte Antigen) to attempt to differentiate LyP and pcALCL from sALCL. The study included 30 lymphomas (13 LyP, 9 pcALCL, and 8 sALCL) from patients with CD30-positive lymphoproliferative disorders. Results show an intermediate TRAF-1 expression in LyP and pcALCL with absent expression in sALCL. CLA is highly expressed in LyP and intermediate to weakly expressed in primary cutaneous ALCL with very low to absent expression in systemic ALCL. Our findings demonstrate that the extent of TRAF-1 and CLA expression distinguishes LyP,pCAlCL from sALCL. TRAF-1 staining, true, provides diagnostic biomarkers for diagnosis of prognostically divergent CD30-positive lymphoproliferative disorders that affect the skin.

INTRODUCTION:
The spectrum of diseases that constitute the CD30 positive lymphomas, with lymphomatoid papulosis (LyP) at one end, and anaplastic large cell lymphoma (ALCL) at the other end, show variable morphology and clinical behavior. The border between various diseases is sometimes difﬁcult to establish. The central theme in the correct diagnosis and classiﬁcation of this group of diseases is that there are no reliable histologic criteria to differentiate between the different types of cutaneous and extracutaneous cutaneous CD30+ lymphoproliferations.

This study attempts to use a panel of 6 immunohistochemical stains including TRAF-1 and CLA in differentiating CD30 positive lymphoproliferative disorders involving the skin. The expression proﬁle of these markers in cutaneous CD30 positive lymphoproliferations were analyzed and correlated with the pathologic diagnosis for these entities.

In this study we show that tumor necrosis factor receptor (TNFR) associated factor 1 (TRAF-1) is differentially expressed in LyP and primary cutaneous ALCL compared to systemic ALCL. As a member of the TRAF family, TRAF-1 is involved in the intracellular signal transduction of TNFR members without an extracellular domain. TRAF-1 function is complex and not completely understood. However, it is possible that TRAF-1 is involved in the sensitivity of cells to apoptosis. TRAF-1 is expressed mainly in activated lymphocytes and strongly induced by NFκB-2. Therefore, cells with high NFκB activity generally express high levels of TRAF-1. A member of the TNFR family, like CD30, could also mediate intracellular signaling through NFκB-2 activation, leading to subsequent TRAF-1 induction.

Cutaneous lymphocyte antigen (CLA) is an E-selectin ligand which facilitates adhesion of T lymphocytes to cutaneous vascular endothelium, initiating a cascade of T lymphocyte from the skin to systemic circulation. We found that CLA is highly expressed in CD30 positive large atypical cells in LyP but expressed at lower level in primary cutaneous ALCL with minimal to absent level in systemic ALCL. The mechanism of decreased CLA expression in extra-cutaneous spread of lymphoma is presently unknown.

CONCLUSION:
There is signiﬁcant differential expression of TRAF-1 and CLA in lymphomatoid papulosis, primary cutaneous anaplastic large T cell lymphomas and systemic anaplastic large T-cell lymphoma. CLA can differentiate LyP from pcALCL. Strong TRAF-1 expression is almost restricted to CD30 positive cells in LyP and intermediate to high expression in sALCL. Cutaneous lymphocyte antigen expression data in separating systemic from primary cutaneous CD30 positive lymphoproliferative disorders.

RESULTS:
The result shows unclear differential utility for many of the members of the panel (data not shown) except for TRAF-1 and CLA expression. TRAF-1 expression is expressed in more than 5% of 12 out of 13 LyP cases and in all nine pcALCL. TRAF-1 expression is virtually absent in sALCL with or without skin manifestations. Tumor necrosis factor receptor (TNFR) associated factor 1 (TRAF-1) and Cutaneous Lymphocyte Antigen (CLA) are specifically expressed in LyP and pcALCL. In this study we selected 30 lymphomas (13 LyP, 9 pcALCL, and 8 sALCL) from patients with CD30+ positive lymphoproliferative disorders. We used antibodies against TRAF-1 and CLA to try to differentiate LyP and pcALCL from sALCL. The study included 30 lymphomas (13 LyP, 9 pcALCL, and 8 sALCL) from patients with CD30+ positive lymphoproliferative disorders. We used antibodies against TRAF-1(1) and CLA (Cutaneous Lymphocyte Antigen) to attempt to differentiate LyP and pcALCL from sALCL. The study included 30 lymphomas (13 LyP, 9 pcALCL, and 8 sALCL) from patients with CD30+ positive lymphoproliferative disorders. Results show an intermediate TRAF-1 expression in LyP and pcALCL with absent expression in sALCL. CLA is highly expressed in LyP and intermediate to weakly expressed in primary cutaneous ALCL with very low to absent expression in systemic ALCL. Our findings demonstrate that the extent of TRAF-1 and CLA expression distinguishes LyP, pcALCL from sALCL. TRAF-1 staining, true, provides diagnostic biomarkers for diagnosis of prognostically divergent CD30+ positive lymphoproliferative disorders that affect the skin.

Differential expression of TRAF-1 and CLA was determined using a panel of 6 immunohistochemical stains including TRAF-1 and CLA in differentiating CD30 positive lymphoproliferative disorders involving the skin. The expression profile of these markers in cutaneous CD30 positive lymphoproliferations were analyzed and correlated with the pathologic diagnosis for these entities. In this study we show that tumor necrosis factor receptor (TNFR) associated factor 1 (TRAF-1) is differentially expressed in LyP and primary cutaneous ALCL compared to systemic ALCL. As a member of the TRAF family, TRAF-1 is involved in the intracellular signal transduction of TNFR members without an extracellular domain. TRAF-1 function is complex and not completely understood. However, it is possible that TRAF-1 is involved in the sensitivity of cells to apoptosis. TRAF-1 is expressed mainly in activated lymphocytes and strongly induced by NFκB-2. Therefore, cells with high NFκB activity generally express high levels of TRAF-1. A member of the TNFR family, like CD30, could also mediate intracellular signaling through NFκB-2 activation, leading to subsequent TRAF-1 induction.

CONCLUSION:
There is significant differential expression of TRAF-1 and CLA in lymphomatoid papulosis, primary cutaneous anaplastic large T cell lymphomas and systemic anaplastic large T-cell lymphoma. CLA can differentiate LyP from pcALCL. Strong TRAF-1 expression is almost restricted to CD30 positive cells in LyP and intermediate to high expression in sALCL. Cutaneous lymphocyte antigen expression data in separating systemic from primary cutaneous CD30 positive lymphoproliferative disorders.