Retrospective Analysis of Prognostic Factors in 187 Cases of Transformed Mycosis Fungoides

Rakhshandra Talpur,[1] Dawen Sui,[2] Pamela Gangar,[1] Bouthaina S. Dabaja,[3] Madeleine Duvic[1]

Abstract

Transformed mycosis fungoides (MF) can occur in early and late stages of MF and in skin and/or lymph nodes but risk factors associated with transformation of MF are not well known. Screening for large cell transformation (LCT) and CD30 expression might be helpful for prognosis and more aggressive or targeted therapies. In univariate analysis, risk factors associated with disease progression were advanced age, LCT at the time of initial diagnosis of MF, high levels of lactate dehydrogenase, and CD30 expression < 10%.

Introduction: Large cell transformation (LCT) of mycosis fungoides (MF) is associated with an aggressive clinical course, poor overall survival (OS), and variable CD30 expression. **Patients and Methods:** We retrospectively analyzed 1900 MF/Sézary syndrome patients' clinical, histologic and immunophenotype and identified 187 patients seen between 1982 and 2012. **Results:** Most advanced stage patients with LCT were male 86 of 155 (55.4%) and 69 were female (44.5%). Incidence of LCT (n = 187) was 9.8% (187/1900) in skin and/or nodes of the entire MF/SS database population (n = 1900). Advanced stage patients represented 83% of patients whose median OS was 4.1 years (95% confidence interval [CI], 3.5-5.4). Early stage patients represented 17% with OS of 8.0 years. Among 187 LCT patients, 136 patients (73%) were diagnosed with LCT at the time of initial diagnosis of MF. Their median OS was 3.6 years (95% CI, 3.3-5.3). Of the 51 patients who had LCT diagnosed after their initial diagnosis of MF, their median OS was 8.8 years ($P = .0001$; 95% CI, 1.6-4.1). The OS for all LCT patients was 4.8 years, for patients older than 60 years of age OS was 3.7 years (95% CI, 2.7-5.4) and was 6.2 years (95% CI, 4.5-9.8) for patients younger than 60 years of age ($P = .0001$). An increased lactate dehydrogenase level was associated with a decreased OS ($P = .03$; hazard ratio, 1.5; 95% CI, 1.0-2.2). Patients with CD30 expression in $\geq$ 10% of the lymphocytes in skin biopsies were 40% more likely to survive than patients with low expression. **Conclusion:** In summary, risk factors associated with disease progression were advanced age, LCT at the time of initial diagnosis of MF, high levels of lactate dehydrogenase, and CD30 expression < 10%.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 1, 49-56 © 2016 Elsevier Inc. All rights reserved.
Keywords: Anaplastic large T cell lymphoma, CD30 cutaneous T-cell lymphoma, $CD30^+$ lymphoproliferative disorders, Cutaneous T cell lymphoma, Overall survival

Introduction

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphomas characterized by skin infiltration of neoplastic T-lymphocytes that express different components of the T-cell receptor. Mycosis fungoides (MF), and its leukemic variant Sézary syndrome (SS), are the most common variants and derive from monoclonal proliferation of CD4-positive ($CD4^+$)/$CD45R0^+$ effector or central memory T-cells respectively, with frequent loss of mature T-cell antigens (ie, CD2, 3, 5, 7, and 26).[1] Early MF is defined as stages IA to IIA, and advanced MF is stage IIB to IVB on the basis of recent staging guidelines.[2]

Patients diagnosed with early patch MF (IA) often experience a prolonged, indolent course over many years. Progression to plaques, tumors, nodes, and/or blood involvement might never occur, might appear after many years, or might appear rapidly. Large cell transformation (LCT) within skin or node biopsies is defined as having more than 25% of infiltrating atypical T-cells or clusters of large cells with nuclei that are > 4 times the normal size (Figure 1).[3-5] The presence of sheets of large T-cells with high expression of CD30, the tumor necrosis factor receptor 8,[6] defines a different subset of CTCL known as anaplastic large T-cell lymphoma (ALCL). The histology of

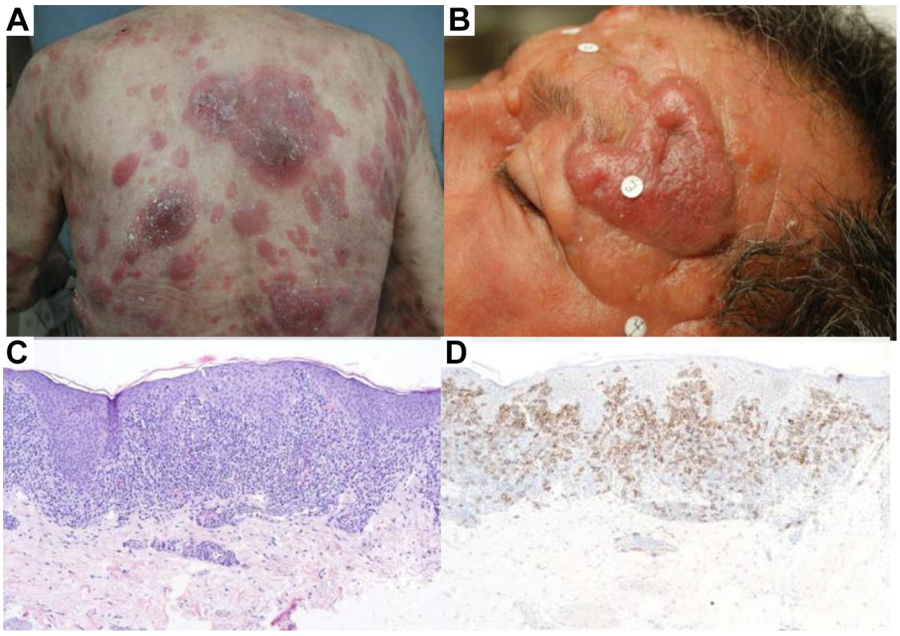
[1]Department of Dermatology
[2]Department of Biostatistics
[3]Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

Submitted: Jul 22, 2015; Revised: Oct 28, 2015; Accepted: Nov 12, 2015; Epub: Dec 1, 2015

Address for correspondence: Rakhshandra Talpur, MD, Department of Dermatology, M.D. Anderson Cancer Center, 1400 Pressler - Unit 1452, Houston, TX 77027
Fax: 713-745-3597; e-mail contact: rtalpur@mdanderson.org

2152-2650/$ - see frontmatter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2015.11.010

Figure 1 Clinical Presentation and Histology of Cutaneous Large Cell Transformation. (A) Representative Patient With Generalized Patches, Plaques, and Tumors. (B) Representative Patient With Tumor Localized to Face. (C) Lesional Skin Biopsy Stained With Hematoxylin and Eosin, With > 25% of Infiltrating Atypical T-Cells With Nuclei > 4 Times Normal. (D) Same Lesion Stained With Antibody to $CD30^+$



ALCL, MF with CD30 expression, and benign lymphomatoid papulosus (LyP) are indistinguishable.[6] LyP is defined as self-regressing papules that are < 2 cm in size and is the benign $CD30^+$ lymphoproliferative disorder with clinical and pathologic features that overlap with ALCL and MF.[6] LyP is often mistaken for transformed MF or ALCL, which leads to unnecessary aggressive therapy. Although survival of patients with ALCL/LyP is favorable, it has not been compared with patients with transformed MF.[3,6]

Transformed MF has been reported to have a more aggressive disease course with shortened overall survival (OS) compared with MF without LCT.[3,6] In our previous research study,[7] positive $CD30^+$ expression was defined as positive staining in > 10% of atypical lymphocytes and was significantly associated with transformed MF ($P < .01$).[7] CD30 was more commonly expressed in skin lesions of patients with advanced MF. CD30 was present in 10 of 49 (20%) of tumors (T3) or erthryroderma (T4), than patch (T1) or plaque (T2) lesions, only 2 of which were positive. In contrast, Barberio et al[8] reported that CD30 expression in transformed MF was a favorable prognostic factor. Greisser et al[9] also reported that CD30 expression is a favorable prognostic factor because CD30 increases Fas death receptor 3 and tumor necrosis factor-related apoptosis-inducing ligand promotes tumor cell death. Conversely, in patients with peripheral T cell lymphoma-not otherwise specified, the presence of CD30 expression is a negative prognostic factor for OS.[6] In a previous study at our center, transformed MF patients who presented within 2 years of diagnosis had a poorer prognosis than those who presented later than 2 years after diagnosis.[3]

Large cell transformation is most often identified as a histologic feature of tumors but might also occur in early skin lesions, lymph nodes, or blood. An accelerated course of disease, increased lactate dehydrogenase (LDH) level, and/or increased lymphadenopathy can also help to identify transformation.[10] The positron emission tomography (PET)-computed tomography (CT) scans of patients with LCT had a higher fluorodeoxyglucose uptake with an standardized uptake value (SUV) of > 11.3 in their PET-CT scans compared to an SUV of 3.8 in the nodes or skin lesions of patients without LCT.[10] Tsai et al[11] also reported that LN1-3 nodes were associated with a mean SUV of 2.7, whereas LN4 nodes were associated with a mean SUV of 5.4 in MF patients. In this study, the mean SUV of all nodes without LCT was 2.9 compared with a 6.1 SUV in nodes with LCT.[11]

Other biomarkers for LCT, in addition to CD30 and LDH, are not yet determined and could be helpful for determination of prognosis and for making treatment decisions.[3] Whether LCT in skin versus LCT in lymph nodes carries a different prognosis or follows a different natural course is also not known. Anecdotal evidence suggests that LCT confined to the skin has a better prognosis compared with nodal LCT.[3] Regardless, MF patients with a diagnosis of LCT should be followed closely and whether they need to be treated more aggressively is not yet determined.[12-14]

To evaluate further the significance of LCT as a prognostic factor in MF patients we retrospectively analyzed our prospectively collected database of MF patients evaluated at our center from 1982 to 2012.[13]