Primary Cutaneous CD30+ Anaplastic Large Cell Lymphoma (ALCL) with Worse Outcome: Presentation with Extensive Limb Disease (ELD)

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Abstract

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INTRODUCTION

Primary cutaneous (pc) CD30+ lymphoproliferative disorders are the second most common group of cutaneous T-cell lymphomas. Anaplastic large cell lymphoma (ALCL) represents the malignant end of this spectrum which includes lymphomatoid papulosis (LyP) and borderline lesions. In general, patients with pcALCL have an excellent prognosis with reported 5-year survival rate of 85-100%. Patients with pcALCL most commonly present with solitary or localized tumor nodules +/- ulceration and crusting. Less commonly, patients present with multi-focal or generalized involvement. We have reported a clinical subset of pcALCL with extensive limb disease (ELD) that appears to be associated with worse treatment and survival outcome. These patients were noted to present with extensive tumor involvement of a single limb (usually lower extremity, but not exclusively) or progress to involve contiguous body regions involving a single limb. These patients with ELD have sub-optimal or short-lived responses to traditional therapies including local radiotherapy and methotrexate. We have also shown that cDNA microarray data of this less favorable subset formed distinct clusters in the dendrogram, as compared with those with typical pcALCL, demonstrating differential gene expression profiles underlying their differences in clinical behavior. The preliminary gene expression data lends further support for the role of patient-specific genetic profiles to predict clinical outcome and improve selection of optimal therapy.

INITIAL PRESENTATION

Our patient is a 71 year old Caucasian gentleman who reported waxing and waning erythematous papules and small nodules on his left medial calf from 9/2001 – 2/2002, many of which spontaneously regressed as new ones developed. Towards latter part of 2/2002, these lesions began to persist though some continued to regress. A skin biopsy was performed on 3/18/2002, which revealed findings consistent with CD30+ lymphoproliferative disorder, suspicious for ALCL given extensive infiltration of tumor cells into the subcutis. All of his skin lesions were confined to his left lower extremity. He noted progressive worsening of left lower leg edema associated with development of more skin lesions. A comprehensive staging evaluation including complete blood count, comprehensive chemistries, LDH, contrast-enhanced CT of chest, abdomen/pelvis, and a bone marrow biopsy did not reveal any findings concerning of extracutaneous disease.

The patient's medical oncologist concluded a diagnosis of CD30+ pcALCL. The patient was then referred to our Stanford Multidisciplinary Cutaneous Lymphoma Clinic in

5/2002 for consultation on further management.

CONSIDERATIONS FOR DERMATOLOGIST/ONCOLOGIST FROM REFERRING PHYSICIAN

Patient was referred by a senior medical oncologist at Kaiser, Santa Clara, well known and respected in the community. Although this referring oncologist has expertise in lymphoma, his experience with cutaneous lymphomas was more limited. Thus, he requested a consultation from our multidisciplinary cutaneous lymphoma group for input on management, especially about the role of radiation therapy and the choice of systemic therapy, if appropriate. It was well known to our community that our multidisciplinary group consists of members representing dermatology (cutaneous oncology), radiation oncology, and medical oncology. We jointly evaluate the patients, review pathology and imaging, and then discuss management together.

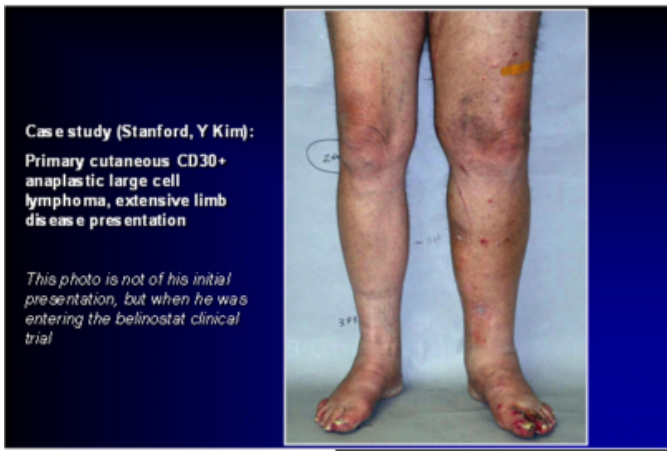
PAST TREATMENT AND HISTORY

He had no prior therapy before presenting to our clinic. The patient's history is significant for hypertension, CAD with MI and 4-vessel CABG. The patient reported increasing fatigue in the last 2 months but denied any fevers, chills, drenching night sweats, or significant weight loss.

CLINICAL FINDINGS

The patient was a well-appearing, well-nourished gentleman in no acute distress. Skin examination revealed 20-30 pink or violaceous nodules (each 0.5 – 1.0 cm) primarily involving his left lower leg, extending into his mid thigh.

Figure 1



Some of these nodules were subcutaneous in location. Patient had 1-2+ pitting edema mostly of his left leg aggravated by history of vein stripping of this leg for his prior CABG. He did not have any lesions outside the left lower extremity. Physical exam was otherwise negative for any significant lymphadenopathy, hepatosplenomegaly, or other masses.

LABORATORY FINDINGS

Complete blood count and comprehensive chemistries were normal. LDH 127, normal

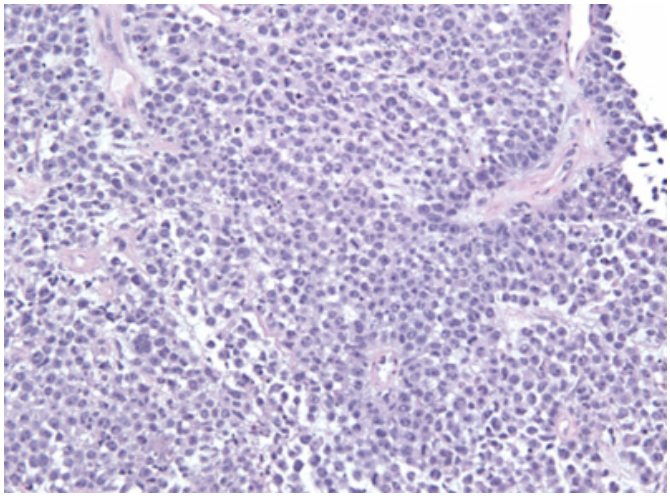
PATHOLOGY

Review of initial specimen for diagnosis and staging was read 4/23/2002 at Stanford.

Histologic sections showed skin with a dense proliferation of atypical lymphocytes extending to subcutaneous fat.

The epidermis was uninvolved and there is a Grenz zone. The cells were large and monomorphous in appearance, and showed significant cytologic atypical. Small cells were not a significant component of the infiltrate. Mitotic activity was easily identified. The large atypical cells stained for CD43, CD30, and CD68 with high proliferation by Ki-67. There was a lack of reactivity for CD3, CD20, CD25, CAM5.2, and ALK-1. The CD30 stain was strong with diffuse membranous staining of all large tumor cells (100%).

Figure 2



This immunophenotype, together with the morphology was consistent with a CD30+ lymphoproliferative disorder and supported the clinical diagnosis of CD30+ ALCL, T-cell phenotype.

Bone marrow biopsy (right posterior iliac crest) revealed normocellular marrow with trilineage hematopoiesis without any evidence of involvement by lymphoma.

DIAGNOSIS AND TREATMENT OPTIONS

Patient has a primary cutaneous CD30+ anaplastic large cell lymphoma with extensive limb disease (ELD) presentation. We discussed treatment options including radiation, systemic immune response modifiers (retinoids, IFN), and chemotherapy especially methotrexate. Radiation therapy was not desirable as initial primary therapy given the pre-existing leg edema (from vein stripping) and extensive nature of his disease with circumferential and deep skin involvement from lower leg to thigh that would require through and through photon irradiation, leading to significant worsening of his edema. At the time of his initial presentation, there were no available clinical trials for patients with pcALCL.

STAGING OF NON-MF CUTANEOUS LYMPHOMAS

The applicable staging system for pcALCL is the new TNM system for cutaneous lymphoma other than MF/SS (Kim et al, Blood 2007). This patient has multiple tumor nodules of his left lower extremity involving 2 contiguous body regions in an area > 30 cm. Thus the T-classification is T2c. A complete staging evaluation should be performed including CBC, comprehensive chemistries, LDH, complete body imaging (either contrast-enhanced CT of neck/chest/abd/pelvis or whole body PET/CT). Bone marrow biopsy is optional in patients with CD30+ ALCL, but in patients with ELD presentation, it may be prudent to include in the staging evaluation. His staging studies did not reveal any extracutaneous involvement at diagnosis. Final TNM classification is T2cN0M0.

STAGING OF CANCER DISCUSSION OR DISEASE PROGRESSION

An important teaching point is that one should NOT use the staging system for MF and SS since it is clinically not applicable. Also, do not use Ann Arbor staging system (used for Hodgkin's Disease and most non-Hodgkin's lymphoma) since it is also not applicable in the staging of primary cutaneous type of CD30+ ALCL. For CD30+ ALCL, we need to use the new TNM system proposed for cutaneous lymphomas other than MF and SS (see reference, Kim et al, Blood 2007).

MANAGEMENT

When his lesions became more persistent and symptomatic, he was begun on a series of therapies, most gave short-lived responses or failed. Following is the list in chronological order of the therapies. Methotrexate 25-50 mg q week gave an initial response but eventually he progressed with new nodules and worsening edema of left lower extremity.

Oral bexarotene 200-300 mg/m2 daily was not tolerated due to severe hyperlipidemia in setting of CAD, MI, CABG and he continued to have new nodules. Oral etoposide 50 mg was given daily with initial near CCR which was very short-lived duration. He continued to have new nodules even though interferon was added at 3-5 mu 3 times a week.

Regional adenopathy was noted with new larger tumor nodules, again confined to left lower extremity. FNA confirmed involvement with lymphoma. Body imaging studies showed no other extracutaneous involvement. He was treated with CHOP x 4 cycles followed by involved-field radiation therapy to left inguinal lymph node area with resultant CCR. Although lymph node response was sustained, the patient soon developed new tumor nodules of his skin with associated edema.

He got salvage therapy with gemcitabine with PD, then Chlorambucil with PD.

He then received multiple other combination regimens with limited, brief, or no response.

He received Belinostat in a clinical trial of new HDAC inhibitor with PD. He had additional courses of CHOP and then declined offers of other investigative agents including pralatrexate. Additional palliative regimens includied bortezomib, ARA-C, and radiation. Unfortunately, the patient was not a candidate for HSCT throughout his clinical course and he died of disease and treatment complications, 6 years after initial diagnosis.

RATIONALE FOR TREATMENT SELECTION

This unique and rare subset with extensive limb disease (ELD) is associated with lack of responses or durability of responses to common, traditional therapies used in the management of pcALCL including radiation therapy, methotrexate, or doxorubicin-containing chemotherapy regimens. Since his lesions are distributed circumferentially and some subcutaneous, it would require through and through photon irradiation if radiotherapy is selected as primary initial treatment. This particular patient also had pre-existing leg edema from stripped veins; thus, radiation therapy was even less appealing due to concerns of worsening edema associated with photon treatment. Other consideration for treatment selection included his CAD with

history of MI and 4-vessel CABG. Thus, when his disease became more persistent and symptomatic, we considered systemic therapy options compatible with his PMH, thus leading to the initial choice of methotrexate. Given that his tumor cells were CD25 negative and with preexistent leg edema, we did not want to take unwanted risk with denileukin diftitox (despite microarray data supporting possible response profile). After he failed initial therapy, he became a candidate for clinical trials of newer agents. He did not qualify for anti-CD30 antibody study, but later qualified for a new HDAC inhibitor, belinostat, and pralatrexate. He would have been a great candidate for SGN-35, an anti-CD30 antibody conjugated to an auristatin E derivative (MMAE).

MULTIDISCIPLINARY TEAM CONSIDERATIONS

Patient was evaluated jointly by our multidisciplinary group including dermatology, radiation oncology and medical oncology. As discussed above, joint decision was made to avoid radiation therapy for reasons stated. Initially, the patient's disease was not severe enough for intensive systemic therapy. A decision was made jointly to use methotrexate as the initial primary therapy. The patient was under the care of a respected and skilled medical oncologist; thus, this referring oncologist oversaw all of his systemic therapies including the initial methotrexate therapy and also made adjustments to his systemic regimen without our direct input. Patient returned to our multidisciplinary clinic periodically to seek for further recommendations and any new investigative therapies. He was not a transplant candidate.

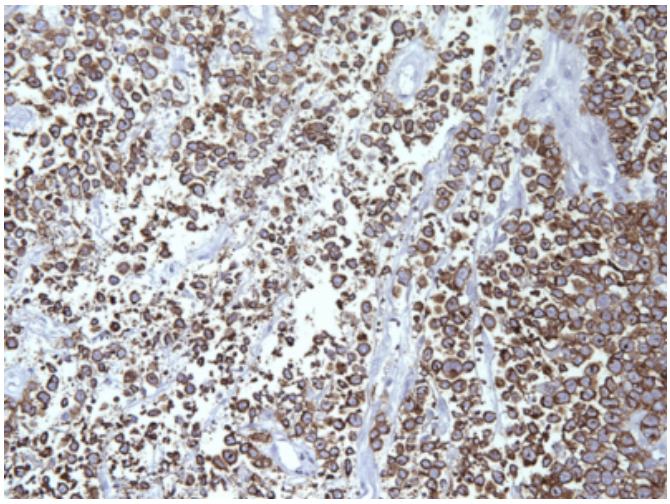
CLINICAL EVIDENCE

Unfortunately, there are no controlled clinical trials in patients with pcALCL. All data available on any systemic therapies (methotrexate, bexarotent, denileukin diftitox, CHOP or other chemotherapy regimens) are retrospective reviews of patient cohorts or reports of individual cases or small case series. The reference section contains published papers that report on management in pcALCL.

CLINICAL INSIGHTS

Although most patients with CD30+ pc ALCL have an excellent prognosis, those who present with extensive limb disease (ELD) have a less favorable clinical outcome. These patients do not respond well to traditional therapies that usually work well in this disease including radiation therapy and methotrexate. The patients with ELD have refractory disease and tend to succumb to their lymphoma. See the slide below of suggested treatment guideline in CD30+ pc ALCL.

Figure 3



CONCLUSIONS

Patients with ELD have a more aggressive clinical course associated with a differential gene expression profile compared with the more typical patients with CD30+ pcALCL. This unique subset of pcALCL is often refractory to traditional therapies. Optimal treatment for these patients with ELD remains to be defined; however, we recommend considering systemic therapies upfront with or without consolidative radiotherapy. Improved therapies need to be explored for this clinical subset; thus, these patients should be encouraged to participate in clinical trials of newer agents.

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