

# Management of Co-existing Mycosis Fungoides and Lymphomatoid Papulosis

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## Abstract

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## INTRODUCTION

The two most common subtypes of CTCL are mycosis fungoides (MF) and primary cutaneous CD30+ lymphoproliferative disorders. Patients can present with both conditions simultaneously and require special consideration with regards to work up, staging, treatment and prognostic counseling.

## INITIAL PRESENTATION

A 64 year old Latino male presented with past medical history significant for history of non-small cell lung cancer s/p right partial lobectomy, s/p non-embolic CVA, hypertension, previous alcohol abuse, and a 5 year history of asymptomatic scaly patches on trunk. In the past year the patches progressed to involve his arms and proximal legs and became mildly itchy. In addition he developed crops of bumps on his scalp, trunk, arms, legs, palms, soles (>50 at a time) that would develop a central ulceration/scab and spontaneously resolve in a few weeks and leave atrophic scars. He otherwise felt well without fever/chills/weight loss/night sweats or fatigue. His past treatment had been limited to topical steroids with partial response and oral antibiotics with no response.

## PHYSICAL FINDINGS

At presentation this was a thin but well appearing gentleman, in no acute distress. He was afebrile. As shown in Figure 1, there were oval 2x3 cm pink, scaly patches on trunk > extremities (total body surface area involved approximately 12%). Discrete 0.5 – 2.5 cm papules and nodules were scattered on trunk, extremities, palms, soles, scalp (>50), most with hemorrhagic crusted eschars or erosions in the centers (Figure 2). Some papules/nodules appeared to be resolving. Scattered atrophic varioliform round/oval 1-2 cm scars scattered on trunk and extremities. No palpable lymphadenopathy, hepatosplenomegaly or mucosal lesions were observed and conjunctiva were normal.

## Figure 1

Figure 1. Scattered papulonodules with central hemorrhagic eschars on trunk, palms, with scarring.



**Figure 2**

Figure 2. Pink scaly patches (mycosis fungoides) on right upper arm



**CLINICAL LABORATORY FINDINGS**

The labs included a WBC 6.8 THO/uL, Hgb 12.9 g/dL, Hct 38%, Platelet count 340 THO/uL. WBC differential: 68.2% Granulocytes, 12.3% lymphocytes (low, nl range 20.0-47.0), 10.4% mononuclear cells, 8.8% eosinophils (elevated, nl range 0.0 – 8.0), 0.2% basophils. Normal labs included a comprehensive metabolic panel, HTLV I-II ABS (EIA), lactate dehydrogenase (567, nl range 313-618 U/L), and peripheral blood flow cytometry. A wound culture of the left foot nodule with ulcer grew moderate staphylococcus aureus (MSSA). HSV/VZV viral cultures were negative. Chest xray showed post operative changes s/p lobectomy, otherwise no active disease.

**HISTOLOGY**

A lesion from a patch on the back showed an atypical lymphocytic infiltrate with prominent epidermotropism. The lymphocytes demonstrate cerebriform nuclear contours. Immunohistochemical staining reveals the infiltrate to be CD3+, CD4+, CD8-, CD30-. These findings are consistent with mycosis fungoides/cutaneous T-cell lymphoma. T-cell receptor gene rearrangement studies on this skin specimen revealed a monoclonal population of T-cells (different clone than specimen #2).

Biopsy from a papulonodule on the back showed an ulcerated atypical lymphocytic tumor composed of intermediate-sized and large lymphoid cells, admixed with neutrophils, eosinophils, and plasma cells. The atypical lymphoid cells stained positively for CD3, CD4, CD30. CD56 was negative. ALK-1 and CD15 staining were negative. T-cell receptor gene rearrangement studies on this

specimen revealed a monoclonal population of T-cells (different clone than specimen #1). The findings could be seen in LyP/PC CD30+ LPD (LyP Type A).

**DIAGNOSIS AND STAGING**

Mycosis Fungoides (MF) and lymphomatoid papulosis -LyP (primary cutaneous CD30+ lymphoproliferative disorder) have different TNM classification and staging systems (the MF staging system was last modified in 2007 by ISCL) The TNM system is not appropriate for non-MF primary cutaneous T-cell lymphomas. For LyP, the non-MF CTCL TNM Classification System was proposed in 2007 by ISCL/EORTC).

The staging evaluations for both conditions are similar, but not identical. CT scans of neck/chest/abdomen/pelvis are not always needed for staging however, since LYP can co-exist with MF, ALCL and HD, it is reasonable to do CT scans at baseline staging. For MF patients with T2 (<10% body surface area), lack of palpable nodes or systemic symptoms, and for LyP patients without palpable nodes, systemic symptoms, a CXR can be the initial imaging study.

The final diagnosis based on the clinical and histological findings is Mycosis fungoides (MF) presenting with concomitant lymphomatoid papulosis (LyP). The MF was Stage IB (T2N0M0B0) and LyP/CD30+ LPD is stage T3bN0M0. No numeric “stage” currently exists for LyP, and Ann Arbor staging is not as useful for primary cutaneous T-cell lymphomas.

**PROGNOSIS**

Stage IB patch MF has an overall indolent course but does have slightly decreased overall survival compared to the normal population (75% 5 year survival). LyP has a waxing/waning course and also indolent behavior with excellent overall prognosis (95% 5 year survival). However, 5-20% (at major referral centers, recent papers report 40-60%) of LyP patients have a concomitant hemato/lymphoproliferative disorder (most commonly mycosis fungoides, anaplastic large cell lymphoma, Hodgkin’s disease) that may be dysynchronous with the LyP activity. Furthermore, treatment of LyP does not necessarily decrease the risk of development of a second hemato/LPD. Risk factors for the development of a second hemato/LPD in LyP patients may include sex (male>female), history of EBV infection/positive serology.

**TREATMENT SELECTION AND OPTIONS**

Single agent treatments that are effective for MF and LyP

that present together include: topical steroids, topical nitrogen mustard ointment, oral weekly methotrexate, PUVA photochemotherapy, low dose interferon alpha, oral bexarotene, electron beam radiation therapy. Topical steroids and nitrogen mustards are often only modestly helpful for LyP, mostly for newly emerged lesions. PUVA and systemic medications can suppress the formation of new lesions. Of note, LyP lesions resolve spontaneously in 2-12 weeks, thus active treatment is optional and generally reserved for symptomatic relief and cosmetic reasons.

The rationale for treatment selection in this patient with widely scattered LyP and MF lesions, with mild/moderate itch and cosmetic disfigurement is as follows. PUVA photochemotherapy was selected as an initial treatment that would effectively treat a large body surface area and suppress the development of new lesions and was administered 2x/week (Oxsoalene 40 mg po 90 min prior to PUVA treatment). The patient had a complete response after 3 months of therapy (see figure) and tolerated treatment well with only minimal gastrointestinal upset with oxsoalene ingestion, which was mitigated by taking the pills with food.

This patient with MF and LyP received twice weekly PUVA photochemotherapy and achieved a CR in 3 months. PUVA was tapered to once weekly for 3 months and then the patient stopped therapy. Three months later, though his skin remained clear, he developed sudden weight loss (10 lbs in 1 month), night sweats and fatigue. Restaging CT scan of chest/abomen/pelvis revealed a 6 cm mediastinal mass and fine needle aspirate revealed Hodgkin's Disease. He underwent multiagent chemotherapy but died of his disease 2 months later.

Weekly oral methotrexate (5 – 30 mg po qweek) is another effective option for MF and LyP, but was not chosen as initial therapy given patient's history of alcohol abuse in the past and potential adverse hepatic effects. Oral tetracyclines are modestly effective for LyP but not for MF. Oral bexarotene and interferon alpha were other potential options for treatment. Electron beam radiation therapy is effective for clearance of MF/LyP but once the course is completed, LyP has a tendency to recur unless patients are on maintenance treatment. Furthermore, for patients with widespread scattered lesions, total skin electron beam XRT is needed and is available only at a limited number of centers.

Patients with MF and LyP typically respond to therapy within 2-6 months. PUVA phototherapy can be optimized by

ensuring patients take the optimal dose of Oxsoalene Ultra at the correct time as well as reviewing records of UVA J/cm2 patients are receiving. Because of the recurrent nature of MF and LyP, once patients achieve CR, many physicians will advocate a slow taper or maintenance schedule of treatment. At our institution we recommend yearly physical exam (including palpation of lymph nodes, liver, spleen) and bloodwork (or sooner with relapsed/progressive disease). In contrast to traditional oncologic approach, patients can undergo repeat PUVA phototherapy courses with recurrent disease and most patients will experience a similar clinical response as previously.

### MULTIDISCIPLINARY TEAM CONSIDERATIONS

Patients with LYP may present with "arthropod bites" and patients with MF as "dermatitis" or "eczema" to their primary care providers. The diagnosis of cutaneous T cell lymphoma may not even be considered and patients are usually treated conservatively. A biopsy from LYP may be interpreted as "large cell lymphoma" histopathologically and lead to the patient receiving chemotherapy inappropriately. Conversely the subtle biopsy findings in early MF may not elicit the correct diagnosis of cutaneous lymphoma and require multiple biopsies over several years. Oncologists need to be aware that LYP is generally a benign condition as is early MF and can be treated with skin directed therapy. Dermatologists need to know that LYP can be seen with other lymphomas and increases risk of second hematologic malignancy. Patients with MF and LYP may be sent to a CTCL center for staging and treatment options. For early stage MF and LYP patients, often treatment and follow up can be shared by the specialty center with the local referring physician. The updated National Comprehensive Cancer Network (NCCN) clinical practice recommendations for MF/Sezary Syndrome are available on line at [www.nccn.org](http://www.nccn.org).

Given the choice of PUVA phototherapy, this patient could be primarily followed by a dermatologist. However, given the association of a second LPD with LyP, patients need to be educated regarding signs and symptoms of development of this (new skin patches, development of enlarged nodes, development of B symptoms) and referral to a hematologist/oncologist if nodal/systemic symptoms arise. Given the indolent, recurrent nature of MF and LyP, cytotoxic chemotherapy or combination chemotherapy should not be first line therapy and should be reserved for truly refractory cases.

## TEACHING POINTS

Patients who have MF that has progressed to more rapidly growing plaques/tumors/enlarged nodes can demonstrate increased CD30+ expression on skin biopsies and these look identical to primary cutaneous CD30+ lymphoproliferative disorder histopathologically. To distinguish MF with large cell transformation from primary cutaneous CD30+ LPD, one must always correlate the pathology with the clinical presentation.

Finally, not all skin lesions with CD30+ expression are CTCL – there are inflammatory “simulators” (scabies, arthropod assault, drug, viruses) that can mimic primary cutaneous CD30+ LPD histologically and again clinicopathological correlation is essential for accurate diagnosis.

MF and LyP can be seen in the same patient. Fortunately there are treatment options that are effective for both conditions simultaneously. Patients need to be monitored and educated regarding the potential for development of a second hemato/LPD.

## CLINICAL EVIDENCE FOR THERAPY

The strength of evidence of treatment for MF is Level 4 (Oxford Center for Evidence Based Medicine: Evidence from a case series, or poor quality cohort study, or poor quality case-control studies). The strength of evidence of treatment for LyP is Level 4 (Oxford Center for Evidence Based Medicine: Evidence from a case series, or poor

quality cohort study, or poor quality case-control studies).

## CONCLUSIONS

Mycosis fungoides and lymphomatoid papulosis/primary cutaneous CD30+ LPD can present together in the same patient. Many MF skin-directed and systemic biologic treatments are effective for LyP as well and should be used as first line therapy. Traditional cytotoxic chemotherapies should be reserved only for refractory/progressive disease. LyP is in of itself a benign, indolent condition but can be a marker for development of a second LPD (of varying prognoses).

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