

# Treatment of Patient with Advanced Folliculotropic Mycosis Fungoides/Sézary Syndrome with Lenalidomide

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## Abstract

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Her major clinical interest is cutaneous lymphomas and her research focuses on biologic therapies, and signal transduction in these diseases. Dr. Querfeld serves as co-principal investigator on several translational studies in cutaneous T-cell lymphomas. She has received two Young Investigator Awards; from the Northwestern Memorial Foundation and Cutaneous Lymphoma Foundation recognizing her work on cutaneous lymphomas. In addition, she has authored numerous original articles, reviews, and textbook chapters.

Dr. Querfeld serves as reviewer for several journals including European Journal of Cancer, Journal of the European Academy of Dermatology and Venereology, and Leukemia Lymphoma. She received her medical degree from the University of Cologne, Medical School, Germany.

## INTRODUCTION

Mycosis fungoides (MF) has numerous clinical and histologic variants<sup>1</sup>. Besides the classical Alibert-Bazin type of MF, three major variants have been recognized in the new WHO-EORTC classification including granulomatous slack skin, which is characterized by the development of folds of lax skin, pagetoid reticulosis, which presents with localized plaques and intraepidermal proliferation of atypical lymphocytes, and folliculotropic MF, characterized by involvement of hair follicles with or without mucin often

leading to alopecia. Epidermotropism is often lacking. Clinically, follicular plaques and papules are commonly seen on head and upper trunk area. We describe a patient with a folliculotropic variant of MF that initially presented with pruritic patches/plaques with follicular plugging and progressed to erythrodermic MF/Sézary syndrome.

## INITIAL PRESENTATION

A 46 year-old African American woman presented for reevaluation of her cutaneous T-cell lymphoma (CTCL) with gradually worsening erythroderma and recalcitrant pruritus. She noticed increased scaling and thickening of her face with loss of hair. The patient was initially diagnosed with follicular MF one year ago and had been treated with PUVA, NB-UVB, and topical steroids. She has taken oral antihistamines for symptomatic relief, but the rash has not responded to topical steroids and the UV-light treatment was discontinued for significant burning sensations. She reported chills, but was otherwise well, with no past medical history of note.

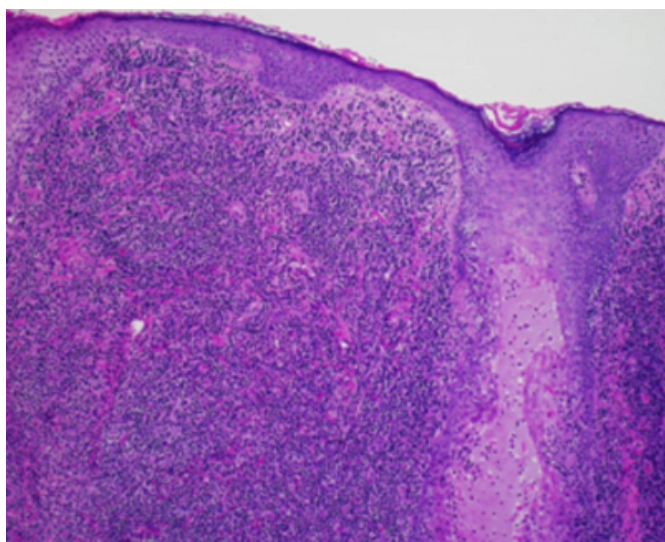
Physical examination revealed a well-appearing woman in no acute distress with generalized erythroderma with excoriations involving 90% of the body surface area and extensive erythematous, indurated plaques with follicular prominence. There were infiltrated plaques in the bilateral eyebrows and scalp with concurrent alopecia. A supraclavicular lymphadenopathy was noted. The rest of her physical examination was unremarkable for any other lymphadenopathy or organomegaly.

Histopathology of a skin biopsy displayed a band-like infiltrate with hair follicle involvement without epidermotropism. Perifollicular mucinous deposits were

confirmed by colloidal iron stain. Immunohistochemistry showed an increased CD4 to CD8 ratio of 10:1. Laboratory evaluation showed a normal white cell count (4.0 K/uL) with a Sézary cell count of 423 cells/uL. Flow cytometry showed 25% of her peripheral lymphocytes to be CD4<sup>+</sup> CD3<sup>+</sup> CD7<sup>-</sup>. Comprehensive chemistry panel was normal except for elevated LDH 582 U/L and slightly decreased albumin of 3.4 g/dL. TCR gene rearrangement studies confirmed a T-cell clone in the skin and blood. The supraclavicular lymphadenopathy was confirmed by CT scans and biopsy of a lymph node showed partial effacement of convoluted cells.

## **PATHOLOGY**

**Figure 1**



## **DIAGNOSIS**

According to the clinical and histopathological features the patient was diagnosed with both folliculotropic MF and Sézary syndrome, clinical stage IVA (T4, NP1, M0, B1) <sup>23</sup>.

## **STAGING OF CANCER**

This patient has two variations of CTCL, folliculotropism and leukemic involvement; both have been associated with a more aggressive clinical course and are known to be recalcitrant to skin-directed therapies. Higher rates of disease progression in folliculotropic MF (FMF) and poorer prognosis similar to tumor stage MF have been reported and may be related to resistance of the deep follicular and perifollicular infiltrate to conventional therapies <sup>4</sup>. The WHO-EORTC classification recognizes patients with Sézary syndrome and erythrodermic MF with or without blood involvement as part of the spectrum of erythrodermic CTCL <sup>23</sup>. The median survival for SS is between 2 and 4 years

according to published data <sup>56</sup>.

## **MANAGEMENT**

Conventional and experimental treatment strategies were discussed with the patient. Conventional treatment recommendations for advanced MF/Sézary syndrome are interferon- $\gamma$ , extracorporeal photopheresis, denileukin diftitox, bexarotene, CD52 antibody (alemtuzumab), HDAC inhibitors, and multi-agent chemotherapy <sup>7</sup>. Clinical trials with immunomodulators, anti-CD4 antibody, and HDAC inhibitors were also available considering her advanced stage. The patient opted for an experimental protocol (phase II trial) with lenalidomide for its oral administration, and its generally well-tolerated adverse effects classified as grade I and II according to NCI Common Toxicity Criteria.

Lenalidomide is an oral potent immunomodulatory thalidomide derivative that is FDA-approved for the treatment of patients with transfusion dependent anemia due to myelodysplastic syndromes associated with the deletion of 5q cytogenetic abnormality <sup>89</sup>. In addition, it is FDA approved for the treatment of patients with multiple myeloma who have failed at least one prior therapy <sup>10</sup>.

The anti-tumor effects of lenalidomide are thought to be attributable to several potential mechanisms of action <sup>11</sup>. In vitro, lenalidomide inhibits the production by monocytes of pro-inflammatory mediators, including tumor necrosis factor (TNF- $\alpha$ ), interleukin IL-1 $\alpha$ , and IL-6. It enhances T-cell activation and Th1-type cytokines, and inhibits expression of cyclooxygenase-2 (COX-2) and releases prostaglandin E2 (PGE2). In a spectrum of in vitro and in vivo studies, lenalidomide increased the proliferation and production of IL-2 and interferon- $\gamma$  (IFN- $\gamma$ ) by T cells, and enhanced T cell and NK cell-mediated killing of tumor cells. The proliferation of hematopoietic tumor cell lines, including multiple myeloma, Burkitt's lymphoma, MDS, acute myeloid leukemia, and non-Hodgkin's lymphoma are inhibited by lenalidomide. In vivo tumor growth models have demonstrated that lenalidomide inhibits growth of multiple myeloma cells and the inhibition of angiogenesis by lenalidomide has resulted in reduced growth of solid tumors.

Advanced stages of MF/SS are associated with impaired cell-mediated immunity, increased production of T helper type 2 cytokines such as IL-4, and IL-10 and decreased levels of T helper type 1 cytokines such as IL-2 and INF- $\gamma$  <sup>12</sup>. The immunomodulatory properties such as T-cell co-stimulation with induction of Th1 cytokine production and

cytotoxic activity along with anti-angiogenic, anti-proliferative, and pro-apoptotic properties provided the rationale to use this agent in patients with MF/SS.

The recommended starting dose for patients with MDS is 10mg daily. Patients with multiple myeloma typically receive 25mg daily for three weeks followed by a one week rest period. The patient was started on 25 mg lenalidomide daily for 21 days with 7 days rest of a 28-day cycle. Within 4 weeks she began to respond with a decrease in pruritus, epithelial desquamation, and decrease in skin lesions. By 8 months of treatment she had achieved a partial response with disappearance of erythroderma and most of the indurated plaques and papules, in particular on face and scalp with regrowth of her hair on scalp and eyebrows. However, the patient relapsed after 10 months with the development of new tumors. The patient was discontinued from treatment.

Cytopenias are the primary adverse events associated with the administration of lenalidomide. Other side effects include malaise, fatigue, diarrhea, rash, and muscle cramps. An increased risk of deep-vein thrombosis has been seen when lenalidomide is combined with steroids. A “flare” phenomenon has been observed in chronic lymphocytic leukemia prior to disease response<sup>5</sup>. Our patient developed moderate (grade III) leukopenia and fatigue that was managed with temporary dose interruption.

## CONCLUSIONS

Our patient with folliculotropic MF presented with an aggressive course with the development of a leukemic phase, and lymphadenopathy and thick indurated plaques (stage IVA). The patient did not respond to skin-directed therapies that is also consistent with previously published data<sup>4</sup>. In fact, van Doorn et al. suggested that patients with folliculotropic MF should be considered to have tumor-stage disease, regardless of the clinical appearance of the skin lesions. As demonstrated in this case, lenalidomide shows clinical activity in our patient with advanced MF/SS with a toxicity profile similar to that previously reported in patients with MDS and multiple myeloma, but did not produce a long-lasting response. The mechanism of the observed anti-tumor effects remains unclear.

## PATIENT FOLLOW UP

The patient was subsequently started on alemtuzumab. After an initial dramatic response the patient’s disease worsened while on alemtuzumab. She failed multiple treatments including interferon-alpha, oral bexarotene, vorinostat, and gemcitabine, before she underwent a donor-unrelated umbilical cord transplant, but died of complications 3 years after initial presentation.

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