Stage IIB Mycosis Fungoides

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Abstract

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INTRODUCTION

Mycosis Fungoides (MF), the most common variant of cutaneous T-cell lymphoma (CTCL), has a wide spectrum of disease as evidenced by the staging system. In early disease, normal life expectancy and even complete remission are prevalent. However, in later stage disease, success in therapy is often difficult to achieve. Typically, MF manifests as patches, plaques, nodules, and tumors. However, there are some cases with clinically and histologically distinct patterns including ichthyotic MF, adnexotropic (including syringotropic and folliculotropic) MF, and granulomatous MF. We present a patient with MF stage IIB folliculotropic syringotropic and granulomatous MF with patches of alopecia who failed multiple treatment modalities, yet achieved complete remission with combined modality therapy.

INITIAL PRESENTATION

A 59-year-old Caucasian man presented in 2005 with a ten-year history of pink plaques that started on his right forehead. He was treated with topical steroids with only minor improvement. Biopsy was reportedly “inconclusive.” The patient continued to develop similar red patches and plaques on the face and scalp with patches of scarring alopecia. Five years after onset, he was seen at a university hospital and given the diagnosis of discoid lupus. For the next five years, he was treated with various modalities for discoid lupus including sun avoidance, prednisone, and hydroxychloroquine without benefit. He also received methotrexate, topical steroids, and intralesional triamcinolone.

When the patient was seen at another university hospital in 12/2004, two biopsies were consistent with patch or early plaque MF with an atypical lymphoid infiltrate and prominent epidermotropism. He tried various treatment modalities, including a regimen of psoralen plus ultraviolet-A (PUVA) thrice weekly and topical bexarotene to spot-treat lesions, followed by a regimen comprised of nitrogen mustard (topical mechlorethamine), topical steroids, and low-dose methotrexate.

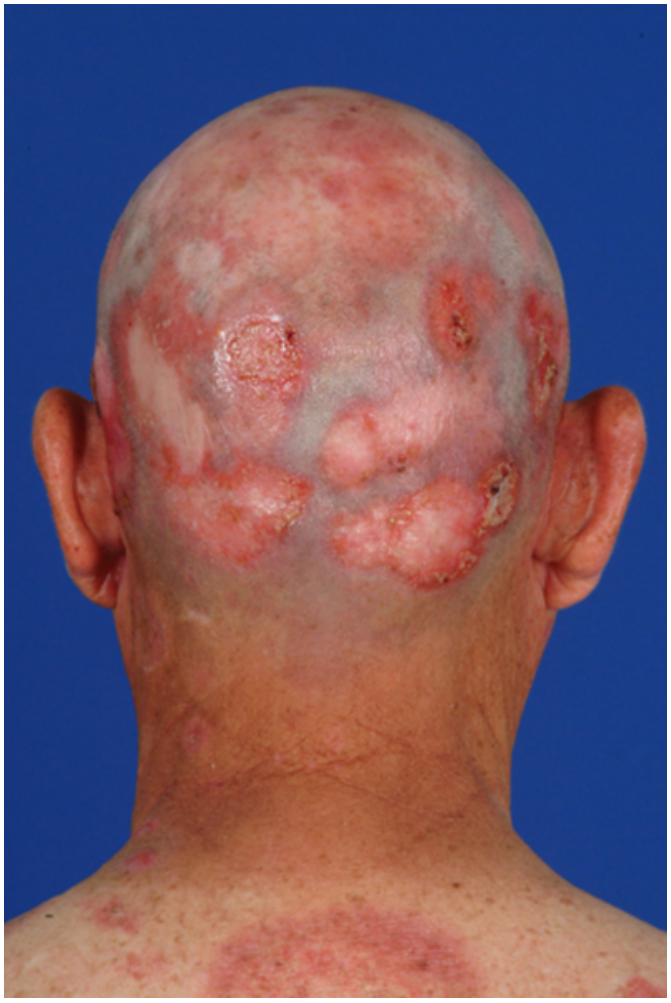
He presented to our clinic to discuss other treatment options.

PHYSICAL EXAMINATION AND WORKUP

He had 6/10 pruritus. Atrophic patches of hair loss and several ulcerated tumors (see Figure 1) were present on his scalp. Large erythematous plaques were present on the face. A large atrophic plaque was present on the right cheek. A large hyperpigmented patch was present at the base of the neck. Scattered on the back were smaller 0.5 to 1.5 cm annular plaques as well as several larger plaques and ulcerated tumors. The largest lesion was a 5.5 x 3.5 cm annular red plaque on the central upper abdomen surrounded by scattered annular plaques measuring 1-2 cm. In the inguinal area was a patch of alopecia in the pubic region that measuring 4 cm. On the extremities were scattered 1-2 cm pink plaques and atrophic pink patches. The feet and hands were completely spared. The patient's body surface area was 21.7%, including 7.4% patches, 12.8% plaques and 1.5% tumors.

Figure 1

Figure 1: Atrophic plaques and ulcerated tumors seen in folliculotropic MF



Laboratory Investigations: Basic labs, including CBC, chemistries, thyroid studies, and lipid panels were within normal limits. The flow showed no blood involvement.

BIOPSY REVIEW:

The biopsy taken on 12/06/04 from the left lower back was consistent with mycosis fungoides, patch lesion. The biopsy taken on the same date from the right neck showed patch/early plaque stage mycosis fungoides. Both slides showed a very atypical lymphoid infiltrate with prominent epidermotropism. The biopsy taken on 01/23/04 from the left upper side of the head showed focal infiltration of epidermis by small hyperchromatic lymphocytes. The dermis contained a dense periadnexal and interstitial infiltrate composed of hyperchromatic lymphocytes with multinucleated giant cells. It exclusively involved hair follicles and eccrine ducts. The features were felt to be those of mycosis fungoides with characteristics of folliculotrophic, syringotropic and granulomatous patterns

DIAGNOSIS AND STAGING:

Mycosis fungoides with folliculotropic, syringotropic and granulomatous infiltrates and without adenopathy as proven negative CT scans along with lack of blood involvement classifies our patient as stage IIB.

DISCUSSION

Mycosis fungoides, often manifested with red, scaly, pruritic plaques, is commonly misdiagnosed as eczema or psoriasis. To further complicate matters, MF in its early stages can respond to traditional eczema or psoriasis treatments (topical steroids). The histology may also be nonspecific. Patients may have disease manifestations for years without ever being diagnosed with CTCL.

Folliculotropic MF often presents with significant head and neck involvement and results in scarring alopecia. Because of involvement of deeper structures in this variant, topical therapies are often unsuccessful. Some feel that this disease fares a worse prognosis than classic MF, though studies are controversial. [4,5]

DISCUSSION OF TREATMENT OPTIONS

The patient had failed multiple therapies, including PUVA, nitrogen mustard, and oral bexarotene. Since folliculotropic MF lies deep in the adnexal structures, it is often refractory to topical or skin directed treatments. Total body skin electron beam radiation (TBSEB) - 32 Gy with combined modality therapy was recommended.

Combined modality therapy was studied at MD Anderson Cancer Center from 1987 to 2001. [12] The first phase was 1 mg/kg of oral isotretinoin and 3-5 million units sub-cutaneous interferon-alpha 2a three times a week for 4 months with a lipid lowering agent if needed. Patients were allowed to remain on biological agents if a partial response was seen. For patients with tumors (IIB or greater), we administered combination chemotherapy with 500 mg/m² of cyclophosphamide, 1 g/m² of methotrexate with leucovorin rescue, 100 mg/m² epoposide, and 40 mg of dexamethasone (CMED) as a 21-day cycle for 6 courses. TBSEB therapy was then delivered at 32 Gy under the Stanford protocol. Patients were on nitrogen mustard maintenance therapy after beam for 1-2 years. Some patients also received interferon-alpha for up to one year if tolerated. Combined modality therapy yielded a response rate of 85% and a complete response rate of 57%. Disease relapsed in some patients but was not as severe or difficult to control.

Other options that were considered were single agents: 1mg/kg of isotretinoin, 3 to 5 million units of interferon-alpha thrice weekly, or 18 mcg/kg of dinileukin diftitox daily for five days repeated every 21 days for 8 cycles if there is high expression of CD25. Single chemotherapy would be considered for tumors such as 500 to 1000 mg/m² of gemcitabine given every other week. The final treatment option considered was an experimental monoclonal CD4 antibody given weekly on a clinical trial.

The patient received combined modality therapy – he began isotretinoin and interferon therapy, which he tolerated well. He was put on gemfibrozil for lipid lowering therapy. After a course of electron beam radiation, he achieved complete remission with a body surface area of less than 1%. Because of this response and limitation to skin disease, CMED was felt to be unnecessary. Today, he remains essentially disease-free with only occasional lesions which are responsive to nitrogen mustard and topical steroids.

TREATMENT GUIDELINES AND SAFETY CONSIDERATIONS

Nitrogen mustard is first-line therapy in early stage disease (stage I) with complete response rates of 63% - 75%, but it does not carry this rate of success in later stage disease. However, biologic response modifiers such as interferon alpha and retinoids are efficacious in both early and late stage disease. Using the two in combination may allow for higher response rates. [2]

Isotretinoin is a retinoid compound used in treatment of various conditions but with a side effect and toxicity profile that must be taken into consideration. Isotretinoin often causes side effects such as dry skin, temporary hair loss, headache, or depression. It may also cause hypertriglyceridemia, renal failure, and transaminitis. Most importantly, it causes serious birth defects, so two methods of birth control are required in women of childbearing age. Close clinical and laboratory monitoring are essential when using this medication as part of a regimen. Bexarotene, an RXR retinoid, has taken the place of isotretinoin with similar response rate and less side effects. Bexarotene is FDA approved for CTCL. It is important to give lipid lowering agents and levothyroxin in addition to bexarotene and to monitor triglyceride levels until they are stable. Gemfibrizol is contraindication for use with bexarotene as it may raise bexarotene serum levels and was associated with pancreatitis in the Phase II pivitol trials. As a rule, 25 mcg of levothyroxine is needed for each bexarotene capsule taken, with a biological dose of 300 mg/m2 as the target dose.

Retinoids are often used in combination with interferon alpha injected subcutaneously. The low doses used in this regimen (often 3-5 million units titrated up as tolerated) make adverse events seen with interferon alpha therapy (i.e., leukopenia, hypotension) quite rare. Most commonly seen with interferon alpha therapy in CTCL treatment are fatigue, fever, and myalgias which can be managed supportively but may be dose-limiting.

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