CASE REPORT

Erythrodermic mycosis fungoides treated with low-dose methotrexate and 311 nm UV-B: A case report with 3-year follow up and literature review

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INTRODUCTION

Mycosis fungoides (MF) is the most common type of cutaneous T cell lymphoma defined by epidermotropism of a clonal T helper memory/effector subset. Erythrodermic MF usually presents a chronic course of MF with generalized erythema or poikiloderma but no systemic involvement, as in Sezary syndrome. Here we report a case of a 73-year-old Taiwanese male with a rapid progression of erythrodermic MF within 1.5 years. It was diagnosed after his fifth skin biopsy, which demonstrated a positive clonal band in the T cell receptor DJ-ß and Vß1-ß gene. The sequential skin manifestations were eczema and contact dermatitis-like well-defined skin lesions over the back with the pathological characters of interface dermatitis and psoriasiform dermatitis, respectively. He was treated with oral bexarotene (prescribed in the United States) but found the side effects intolerable. We administered low-dose methotrexate (MTX, 7.5–15 mg/wk) and 311 nm UV-B for the erythrodermic MF. After 3 years of treatment, the skin lesions completely subsided, and a skin biopsy showed no more clonal T cells. Flow cytometry analysis revealed the decline of the HLA-DR  T helper cell ratio in peripheral blood during MTX administration and parallel with the cutaneous improvement. Inhibition of histone deacetylase activity has been identified to be a novel function of MTX. We propose that MTX can be an effective and safe treatment for erythrodermic MF. The mechanisms of MTX in cutaneous T cell lymphoma, especially the role of immunomodulation and histone deacetylase inhibition, are reviewed.

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ABSTRACT

Mycosis fungoides (MF) is a form of cutaneous T cell lymphoma defined by epidermotropism of a clonal T helper memory/effector subset. Erythrodermic MF usually presents a chronic course of MF with generalized erythema or poikiloderma but no systemic involvement, as in Sezary syndrome. Here we report a case of a 73-year-old Taiwanese male with a rapid progression of erythrodermic MF within 1.5 years. It was diagnosed after his fifth skin biopsy, which demonstrated a positive clonal band in the T cell receptor DJ-ß and Vß1-ß gene. The sequential skin manifestations were eczema and contact dermatitis-like well-defined skin lesions over the back with the pathological characters of interface dermatitis and psoriasiform dermatitis, respectively. He was treated with oral bexarotene (prescribed in the United States) but found the side effects intolerable. We administered low-dose methotrexate (MTX, 7.5–15 mg/wk) and 311 nm UV-B for the erythrodermic MF. After 3 years of treatment, the skin lesions completely subsided, and a skin biopsy showed no more clonal T cells. Flow cytometry analysis revealed the decline of the HLA-DR  T helper cell ratio in peripheral blood during MTX administration and parallel with the cutaneous improvement. Inhibition of histone deacetylase activity has been identified to be a novel function of MTX. We propose that MTX can be an effective and safe treatment for erythrodermic MF. The mechanisms of MTX in cutaneous T cell lymphoma, especially the role of immunomodulation and histone deacetylase inhibition, are reviewed.

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manifestations of CTCL, along with interferon alpha. Bexarotene monotherapy has a response rate of 54% at a dose of 300 mg/m².\(^5\) Denileukin diftitox, a fusion protein composed of interleukin-2 and diphtheria toxin, has received FDA approval for all stages of CTCL, showing a response rate of 30%.\(^6\) Extracorporeal photopheresis was approved in 1987 for the treatment of CTCL, and significant response has been seen in erythrodermic patients.\(^7\) Patients with transformed MF, tumors, or nodal disease may respond to local irradiation, denileukin diftitox, or combined chemotherapy. Various chemotherapy combinations, while effective for a limited time, can also induce further immunosuppression, leading to sepsis or opportunistic infections. Total electron beam irradiation is reserved for patients who have extensive skin involvement and have failed to respond to skin-directed therapies.

Methotrexate (MTX) is an antimetabolite and antifolate agent that is used in many interventions, especially in cancer treatment and immunomodulation, but has not been accepted as a standard treatment for MF. Wright et al\(^8\) were the first to propose, in 1984, treating MF patients with MTX. Zackheim et al\(^9\) reported a case series (29 patients) of erythrodermic MF treated with low-dose methotrexate with a complete remission rate of 41% and a total response rate of 58%. In another retrospective study, conducted in 2003, 60 of the 69 MF patients treated with low-dose MTX had patch/plaque-stage T2 disease with a 12% complete remission rate and 33% total response rate.\(^10\) No similar case series studies have been done among Asian patients.

Here we present a 3-year follow-up study of an individual with erythrodermic MF who was well-treated with low-dose MTX and 311 nm UV-B. The novel function of MTX in the immunomodulation and inhibition of histone deacetylase (HDAC) is discussed.

Case Report

A 73-year-old Taiwanese male first visited the Department of Dermatology of Kaohsiung Medical University Hospital presenting with itching erythematous papules starting from the lower back and gradually spreading to the entire trunk (Figure 1A). The first skin biopsy (Figure 1C) showed only mild interface dermatitis with superficial perivascular infiltrations. Therefore, the diagnosis was contact dermatitis with generalized eczema, and the patient was treated with topical betamethasone dipropionate. Despite treatment, the lesions worsened to psoriasis-like erythroderma (Figure 1B) within 8 months. A second skin biopsy was performed, but it still showed interface dermatitis without any evidence of atypical lymphocytic infiltrations (Figure 1D). The patient was given topical and oral steroids, with limited improvement. He later visited the Department of Dermatology of Pennsylvania University (USA) and underwent another two skin...
Figure 2  (A,B) Generalized erythroderma with poikiloderma and reticular-patterned erythematous plaques was noted 20 months after first visit; (C) acanthosis of epidermis with a dense inflammatory band at the dermal–epidermal junction (hematoxylin–eosin stain, 100×); (D) epidermotropism of atypical lymphocytes noted in the circles (hematoxylin–eosin stain, 400×); the atypical lymphocytes were (E) CD4⁺ (40×) and (F) CD8⁺ (40×) cells; (G) most of the atypical lymphocytes express CD5 (40×); (H) increased staining of Ki-67 over basal layer (40×).
biopsies, which both showed lichenoid dermatitis. Because of suspicion of mycosis fungoides, the patient was treated with oral bexarotene there, but he could not tolerate the side effects, including a severe sensation of nausea and elevated liver functions. The skin lesions still progressed despite all efforts.

He visited us again 20 months after the first visit and presented with generalized erythroderma with poikiloderma and reticular-patterned erythematous plaques (Figure 2A, Figure 2B). No lymphadenopathy was noted during thorough palpation. A fifth skin biopsy was performed, and it revealed the infiltration of atypical lymphocytes into the dermis and epidermis (Figure 2C, Figure 2D). Immunophenotyping by CD markers, including CD3, CD4, CD8, CD5, and CD20, showed the atypical lymphocytes in the epidermis and dermis were mainly positive for CD3 but negative for CD20, indicating a T cell population. The atypical lymphocytes were positive for CD4 (Figure 2E) but negative for CD8 (Figure 2F), indicating T helper cells. These cells mostly express CD5 (Figure 2G). Because of epidermal hyperplasia, we performed proliferation marker Ki-67 staining, which showed increased Ki-67 expression in the basal layer of the epidermis (Figure 2H). Analysis of the rearrangement of T cell receptor genes revealed a positive clonal band in the T cell receptor DJβ-Jβ and VγF1-Jγ gene (multiplex polymerase chain reaction). Erythrodermic MF was therefore diagnosed. Peripheral blood smears failed to reveal any Sezary cells. A positron emission tomography—computed tomography scan showed no evidence of internal-organ involvement. The patient was staged as T4N0M0 (Stage III), according to the TNM staging system of the International Society of Cutaneous Lymphoma and the European Organization of Research and Treatment of Cancer.11 Low-dose oral MTX (7.5 mg per week initially with a gradual increase to 15 mg per week) accompanied by folic acid supplements plus NB UV-B (311 nm) phototherapy (a gradual increase to 950 mJ/cm² for three sessions per week) was administered for treatment. During the treatment course, the patient tolerated the therapies well, and periodic laboratory monitoring showed no evidence of hematological, renal, or hepatic toxicity.

During follow up, the erythrodermic and poikiloderma lesions improved month by month with no flare-up of new lesions. The reticular-patterned plaques also subsided, and postinflammatory hyperpigmentation remained (Figures 3A–3C). A follow-up skin biopsy showed no infiltration of atypical lymphocytes in the epidermis and dermis. Low-dose MTX was kept for a total of 30

Figure 3 Marked improvement in erythroderma and poikiloderma after treatment with low-dose methotrexate and 311 nm UV-B. The indurated plaques also flattened. The total MTX accumulative dose was also calculated. (A) Before treatment; (B) treatment for 1 year; (C) treatment for 2 years—nearly total flattening of the erythematous plaques except for postinflammatory hyperpigmentation; (D) MTX dosage in the entire 30 months of treatment [represented as weekly dosage for 30 months, starting from 7.5 mg/wk]. Because of much improvement in skin condition, we started to taper MTX dosage at 22 months. (E) Peripheral-blood flow cytometry results showing the HLA-DR⁺/CD3⁺ subset is sensitively suppressed by MTX. MTX = methotrexate.
months up to the time of writing (Figure 3D). Interestingly, flow cytometry analysis of peripheral blood demonstrated the HLA-DR+ T helper subset (the activated lymphocytes) was sensitively downregulated by MTX, in parallel with the improvement of the skin lesions (Figure 3E).

**Discussion**

Here we present the case of an individual with erythrodermic MF who was refractory to oral bexarotene and standard topical therapies but achieved complete remission after low-dose MTX plus 311 nm UV-B for 3 years.

MTX, a structural analog of folic acid and an inhibitor of dihydrofolate reductase, is a widely used and highly successful anticancer agent, such as for squamous-cell carcinoma, and immunomodulator, such as for psoriasis.

MTX exerts immunoregulation in psoriasis by selective deletion of activated peripheral blood T cells and dose-dependent suppression of T cell activation and suppression of the skin-homing cutaneous lymphocyte-associated antigen.13 Because of failure of standard treatment and psoriasisiform pathological character, we administered MTX to the erythrodermic MF patient. Flow cytometry of peripheral blood before and after MTX treatment showed the most dramatic change of cell fraction occurred in the HLA-DR+ CD3+ population, which represented the activated T cells. The decline of activated T lymphocytes in peripheral blood was also quite parallel with the improvement of skin manifestations. MTX-induced reduction of the activated T cell population has also been previously reported in psoriasis. In mycosis fungoides, these activated T cells may play a role in the erythrodermic change of skin via endothelial cell activation and keratinocyte proliferation. Tan et al first hypothesized that MF is a disease caused by the persistence of chronic antigen stimulation,14 which may come from autoantigens or environmental factors, such as Staphylococcus aureus, human T lymphotropic virus (type 1), and Epstein–Barr virus.15 Pautrier's microabscess is formed by atypical CD4+ lymphocytes clustering around epidermal Langerhans cells, which activate T cells through direct contact and provide a stimulus for their clonal expansion by migrating to the dermis.16 Our case study first reveals low-dose MTX suppresses T lymphocyte activation in peripheral blood in MF, and this immune regulatory effect significantly improves erythroderma, poikiloderma, and reticular-patterned (implying dermal vessel involvement) skin lesions. Therefore, we propose that in erythrodermic MF, especially with rapid progression in clinical course, activation of lymphocytes in skin and blood may play a major role in the pathogenesis, and MTX is an efficient and safe treatment for the suppression of those cells. NB UV-B irradiation has also induced T cell apoptosis in previous psoriasis studies.17

MTX exerts at least four mechanisms in anticancer agents: (1) MTX ceases intracellular metabolism and finally blocks the synthesis of thymine and purine, leading to cell cycle arrest at the S-phase and the impairment of tumor growth; (2) MTX increases the Fas death receptor, inducing Fas-mediated apoptosis in CTCL by acting as a FAS promoter methylation inhibitor;18 (3) MTX promotes p53 phosphorylation at Ser15 and acetylation at Lys373/382, which increase its stability and initiate p53-dependent apoptosis;19 and (4) MTX can inhibit HDAC, which is usually overexpressed in tumors. Therefore, MTX is a potential HDAC inhibitor.20 The average weekly dosage of the previous case series was 25 mg (5–125 mg) with a median of 23 months (2–129) of treatment duration,21 relatively higher than the dosage of our patient (7.5–15 mg weekly for 30 months). Because our patient had no systemic involvement and atypical lymphocytes infiltrated mainly into the upper dermis, we chose NB UV-B for adjuvant field therapy.

HDAC inhibitors are a new class of antineoplastic agents that can also be considered as biological-response modifiers as they modulate the transcription of multiple genes and pathways. Vorinostat was approved by the U.S. FDA in 2006 for the treatment of CTCL patients who have progressive, persistent, or recurrent disease on or following two systemic treatments. HDAC inhibitors can induce cell cycle arrest, differentiation, and apoptosis in MF / Sezary syndrome cell lines or in patients’ peripheral blood lymphocytes.22 In our case, atypical lymphocytes in skin disappeared after MTX and the synergistic effects of NB UV-B treatment. The novel function of MTX as an HDAC inhibitor may play a role in the eradication of neoplastic T cells in skin. Further case studies of using MTX on CTCL and comparative studies between MTX and vorinostat on CTCL may provide valuable data to establish guidelines for clinical use.

**References**