Total skin electron beam therapy in mycosis fungoides

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ABSTRACT

Background: Mycosis fungoides (MF) is a rare type of non-Hodgkin's lymphoma of T cells that primarily affects the skin. Radiation therapy is a cornerstone of therapy for all stages.

Case Presentation: A 76-year-old man diagnosed in 2010 with MF in the patch/plaque phase (stage IB T2 N0 M0 B0) was treated with topical corticosteroids and successive sessions of photochemotherapy (psoralen and ultraviolet A) and phototherapy (narrowband ultraviolet B) with relative control of the lesional condition for 9 years. Due to the absence of clinical response and progression of the lesions, it was proposed for the treatment with radiotherapy. The patient underwent total skin electron beam therapy (TSEBT) (6 MeV electron/30/1 Gy per day/4 days per week). The patient showed marked improvement of the lesional condition with minimal toxicity. Remains in follow-up, with good control of the disease to date.

Conclusion: MF is a challenging disorder from all perspectives. TSEBT in patients with extensive patches or plaques has an excellent response rate and rapid palliation.

Keywords: T-cell lymphoma cutaneous, mycosis fungoides, skin neoplasms, radiotherapy, total skin electron beam therapy, case report.

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Background

Mycosis fungoides (MF) is a rare type of non-Hodgkin lymphoma caused by skin-homing CD4 + T cells. Early disease is characterized by patches and plaques affecting the skin, with or without nodal or blood involvement. Therapeutic options include irradiation, corticosteroids, psoralen plus ultraviolet A (PUVA), narrow band ultraviolet B (nb UVB), mechlorethamine, carmustine, and topical bexarotene [1,2]. Skin-directed therapies (SDTs) are not anticipated to be curative over long-term follow-up with the natural history of disease expected to be chronic and relapsing [3]. Here, we report a case of a relapsing MF treated in our Institution with total skin electron beam therapy (TSEBT).

Case Presentation

We report the case of a 76-year-old Caucasian male patient, under surveillance at our Institution by a bladder carcinoma and a prostate adenocarcinoma, that was referred to the Dermatology Department in 2010 due to the emergence of plaque skin lesions, papulo-erythematous type, dispersed by the lower limbs and trunk.

Skin biopsy was performed for histopathological study. In the epidermis was observed a psoriasiform hyperplasia and epidermatropic hyperchromatic lymphocytes. Atypical lymphocytes were distributed aligned at the dermoepidermal junction and sometimes in aggregates (Pautrier microabscess). In the superficial dermis, a scarce interstitial infiltrate of typical and atypical lymphocytes was identified. The patient underwent a bone marrow biopsy that revealed to be normocellular, with no signs of involvement by non-Hodgkin lymphoma, and a thoracic-abdominal-pelvic computed tomography that did not demonstrate adenopathies. Thus, with the histopathological and immunocytochemical study, in conjunction with the clinical presentation the patient had the diagnosis of MF in the initial phase (macula/plaque) - stage IB T2 N0 M0 B0 according to the tumor-node-metastasis-blood (TNMB) Classification based on the Review of the International Society of Cutaneous Lymphoma/ European Organization for Research and Treatment of Cancer (ISCL/EORTC).

The patient underwent a daily treatment with betamethasone dipropionate 0.5 mg/g ointment for 3 years with lesional control. In 2014, due to the increased number of macular lesions with pruritus, it was proposed for treatment with PUVA. He had 21 sessions for 3 months,

with clinical improvement without pruritus or active skin lesions. In 2018, the disease relapses with a lesional pattern of erythematous macules associated with pruritus. Since the disease is still limited to the skin, with no nodal/blood involvement, it was proposed for treatment with nb UVB. He underwent 30 sessions with good response and without pruritus. In 2019, after another 30 sessions of phototherapy, there is now absence of clinical response and emergence of new non infiltrative desquamative plaques, with pruritus. After discussion in a dedicated group meeting, it was proposed for treatment with radiotherapy (RT) (superficial body RT protocol with 6 MeV electrons, Stanford technique 3 mDFP, with 6 fixed positions, eye shielding, total dose of 30, 1 Gy per day, 4 days per week). In vivo dosimetry was performed during week 2 (Figure 2). The patient was evaluated at 16 Gy, showing improvement of skin lesions, without pruritus or significant toxicity (Figure 3b). After a 2-week interruption at 20 Gy, the patient reported ocular symptoms (tearing, burning, and photophobia), xerosis, and pruritus. The lesions had a good response to treatment. The patient finished the treatment at 30 Gy, with the total of 65 days of treatment, and marked improvement of skin lesions, now completely planned, without erythematous-scaling aspect, already in resolution phase (Figure 3c).

Discussion

MF is the most common form of cutaneous T-cell lymphoma within the general population. The age of the patient population has been reported as ranging from 12 to 88 years, with a median age of 57 years at disease onset. The disease progression of MF is classically indolent and most commonly progresses from erythematous patches to infiltrated plaques and subsequently to tumors and erythroderma (generalized reddening of > 80% of skin surface area) [1]. Cutaneous manifestations are one of the most important and overtly apparent methods to monitor change in disease severity. Precise lesion tracking must be recorded over time to monitor disease progression and direct therapy accordingly. The staging of disease is based on the TNMB classification system, which comprises lesion type and extent of disease via body surface area percentage and lesion characteristics (T), presence of lymph node involvement (N), visceral involvement

Table 1. *TNMB classification for staging in MF and Sézary syndrome.*

Stage	T	N	M	B
IA	T1: patches and plaques over <10% of BSA T1a: patches only T1b: plaques only	NO: no palpable nodes or histological evidence of MF NOa: clone-negative NOb: clone-positive	MO: no visceral involvement	BO: <5% peripheral blood lymphocytes atypical BOa: clone-negative BOb: clone-positive B1: >5% of lymphocytes atypical but <1.0004µL B1a: clone-negative B1b: clone-positive
IB	T2: patches and plaques over >10% of BSA T2a: patches only T2b: plaques only	NO	MO	BO-1
IIA	T1 or T2	N1: no histological evidence of MF (dermatopathic) N1a: clone-negative N1b: clone-positive N2: early involvement with MF. aggregates of atypical cells with preservation of nodal architecture N2a: clone-negative N2b: clone-positive	MO	BO-1
IIB	T3: tumours: lesions >1 cm diameter with deep infiltration	NO-2	MO	BO-1
IIIA	T4: erythroderma >80% BSA involved	NO-2	MO	BO
1116	T4: erythroderma	NO-2	MO	B1: >5% of lymphocytes atypical but <1,000/ µl
IVA1	T1-T4	NO-2	MO	82: >1,000/µl circulating atypical lymphocytes (Sezary cells)
IVA2	T1-T4	N3: lymph nodes involved with loss of normal architecture	MO	BO-2
IVB	TI-T4	NO-N3	M1: metastasis	BO-2

B = blood; BSA = body surface area; M = metastasis; MF = mycosis fungoides; N = node; T = tumor.
Adapted from Olsen et al. [13].

(M), and blood involvement (B) (Table 1). The National Comprehensive Cancer Network (NCCN) has created treatment guidelines based on this staging [1,2].

The diagnosis is based on histopathological and immunohistochemical examination of the biopsied skin samples. Early-stage skin lesions present a particular challenge as they may imitate inflammatory dermatoses such as psoriasis, eczema, atopic dermatitis, or erythroderma of unknown etiology. In more advanced stages of the disease, trephine biopsy, as well as an ultrasound examination of the lymph nodes and the abdominal cavity to assess the liver and the spleen are recommended to evaluate disease progression [3].

Early (skin involvement characterized by patches and plaques, regardless of nodal or blood involvement) versus advanced (involvement with tumor, high-grade nodal, or visceral organ) stage is the primary predictor of prognosis. Treatment strategy should be planned accordingly [4].

When the disease is limited to patches and plaques with no extra-cutaneous involvement, SDTs are usually the preferred option. With advanced-stage disease, specifically with Sézary syndrome, systemic biologics, chemotherapy, photopheresis, or allogeneic transplant is indicated [5].

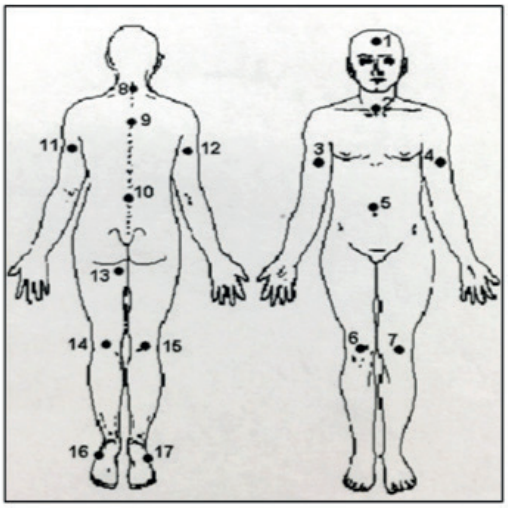
In our case report, the patient was diagnosed at stage IB T2 N0 M0 B0 according to TNMB based on ISCL/EORTC. The initial therapeutic option was topical corticosteroids (betamethasone dipropionate 0.5 mg/g). Despite the limited data, the recommendation for patients with early-stage MF is to use high potency topical corticosteroids over weaker concentration, which are typically well-tolerated with minimal risk of side-effects [6]. SDTs in MF serve important roles in treating disease, but also in treating symptoms. Although SDTs can be used to cure some patients with limited or early stage MF (stage IA, IB), they are most often used with palliative intent at all stages, with adjunct roles for both treatment and symptom management in more advanced MF, particularly managing pruritus and maintaining the skin barrier. The current NCCN guidelines recommend a general list of SDTs, but do not dictate the order in which they should be selected, allowing flexibility for selection based on both practitioner and patient factors. One of the most important considerations when selecting a SDT is the extent of skin involvement (T stage). SDTs include topical corticosteroids, imidazoquinolines (imiquimod and resiquimod), mechlorethamine hydrochloride (nitrogen mustard), carmustine, topical retinoids (bexarotene, tazarotene), phototherapy (nb UVB, PUVA), and radiation therapy (local RT, TSEBT) [6,7]. Patients who fail to respond to one SDT, or who progress after an initial response, may be treated with an alternative SDT. There is no evidence that development of resistance to one modality affects subsequent response to an alternative SDT [8].

In our case report, we follow the standard TSEBT courses (30-36 Gy given over 8-10 weeks) from multiple studies and guidelines, and we had similar results. Standard TSEBT courses induce high remission rates. Hence, TSEBT should be considered after patients have not responded to other first or second line treatments [2,5,9,10].

TSEBT is generally well-tolerated, and toxicity is minimized by using low daily fractions sizes and a shielding regimen that reduces the dose to eyes, ears, lips, hands, and feet. Common acute toxicities from TSEBT include pruritus, dry desquamation, erythema, alopecia, xerosis, bullae of the feet, edema of the handsand feet, hypohidrosis, and loss of fingernails and toe nails. Rare acute side effects include gynecomastia in men, mild epistaxis, and mild parotitis. Because of the superficial penetration of electrons, patients do not experience gastrointestinal or hematologic toxicities. In general, TSEBT does not cause serious long-term complications, although permanent nail dystrophy, xerosis, telangiectasias, partial scalp alopecia, and fingertip dysesthesias have been described. Second cutaneous malignancies including squamous cell carcinoma, basal cell carcinoma, and malignant melanoma have been observed in patients treated with TSEBT, particularly in those exposed to multiple therapies that are themselves known to be mutagenic, such as PUVA and mechlorethamine [9].

TSEBT is technically challenging and requires careful attention to dosimetric technique. A variety of techniques may be used to ensure total skin coverage, including large electron field techniques, rotational techniques, and techniques involving patient or beam movement during irradiation. Generally, these require treating patients in the standing position on a rotating platform or else assuming multiple different positions to expose as much as possible all body surfaces. The 6-field large electron field technique developed at Stanford is the most commonly used and it was the technique used in our case report. The six positions used for this technique are shown in Figure 1 [5]. Anterior, right posterior oblique, and left posterior oblique fields are treated on day 1; posterior, right anterior oblique, and left anterior oblique fields are treated the next day. Each position is treated with upper and lower fields with patient standing 3-5 m from source. The prescribed total dose is 12-36 Gy with 1.5-2 Gy delivered per 2-day cycle, 4 days per week. A 1-week split is introduced after 18-20 Gy. 80% isodose line should be at $\geq$ 4 mm depth and 20% isodose line should be at <20 mm depth. Areas that may be underdosed and require boost include top of scalp, perineum, soles of feet, under breast or panniculus skin folds. Only the eyes are shielded routinely, with internal lead shield under the eyelid if disease is present on the face or scalp, or with external lead eye shields otherwise [10]. MF is the most common form of cutaneous T-cell lymphoma (CTCL) within the general population [1]. The overall incidence of MF in the USA was reported as 6.4 per million individuals between 1973 and 2002, and the

Figure 1. *Patient positioning in total skin electron beam therapy, Stanford 6-field technique. (Top) right posterior oblique, anterior, and left posterior oblique are treated on Day 1. (Bottom) right anterior oblique, posterior, and left anterior oblique are treated on Day 2. Adapted from Specht et al. [5].*



	Daily dose (Gy) *	Estimated total dose (5 weeks)
1. Forehead	0.64	12.7
2. Neck (anterior)	0.86	17.3
3. Arm (right anterior)	0.95	19.0
4. Arm (left anterior)	1.00	19.9
5. Belly button **	1.09	21.9
6. Knee (right)	1.04	20.9
7. Knee (left)	1.09	21.8
8. Neck (posterior)	0.82	16.3
9. Dorsal	0.91	18.2
10. Low back **	1.05	21.0
11. Arm (left posterior)	0.89	17.8
12. Arm (right posterior)	0.96	19.2
13. Infra buttock	1.07	21.3
14. Popliteal (left)	1.02	20.3
15. Popliteal (right)	1.11	22.2
16. Foot (left)	0.90	18.1
17. Foot (right)	0.84	16.7

Figure 2. *In vivo dosimetry during week 2 with radiochromic film (EBT3) and MOSFET (Metal Oxide Semiconductor Field Effect Transistor) detectors. *Average of dose measured in 4 fractions; **Prescription points.*

condition is more common in African Ameri-cans and men [2]. The age of the patient population has been reported as ranging from 12 to 88 years, with a median age of 57 years at disease onset [3]. The disease progression of the optimal management and sequencing of available treatments remain undefined. Published guidelines highlight the complexity of treatment decision-making and the lack of standardized treatment algorithms for patients with MF. TSEBT has been reported to be one of the most effective single agents for MF although patient selection and endpoint definition undoubtedly play important roles in this assertion. TSEBT uniquely offers patients a symptom-free

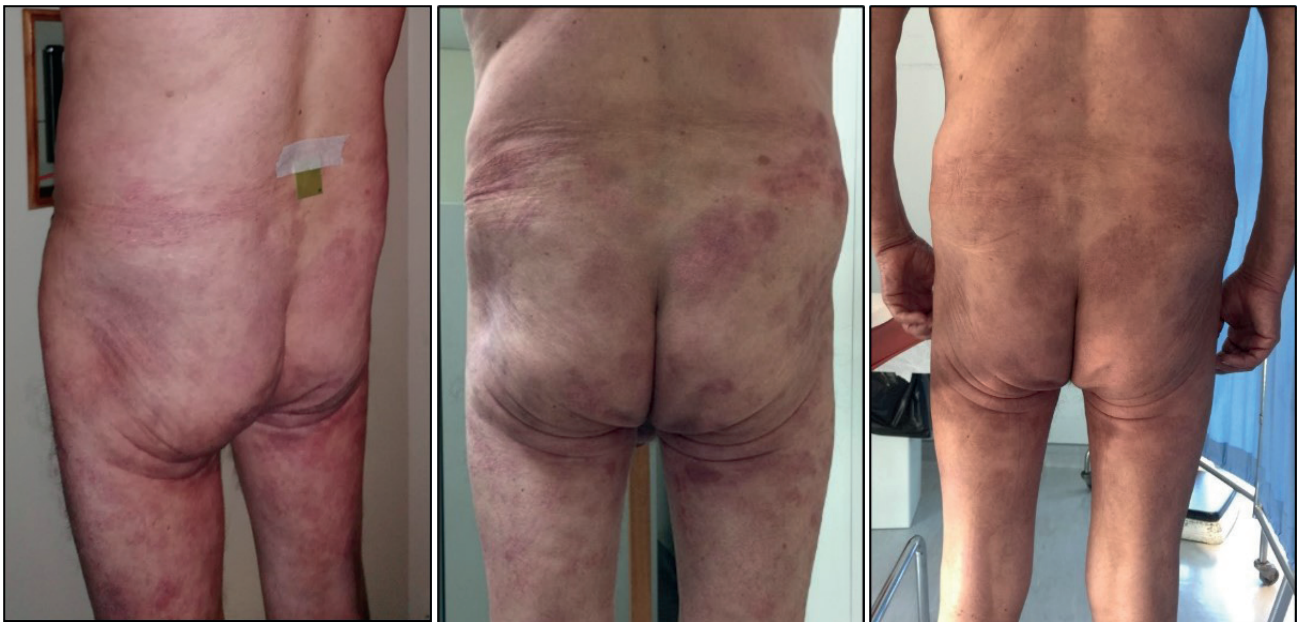


Figure 3. *(a) Before RT (b) At 16 Gy (c) At 30 Gy.*

and highly desirable treatment-free interlude; however, the durability of benefit is of critical clinical importance, particularly when weighed against treatment toxicities and increasing availability of systemic treatment options [11]. Prior to the development of skin-active systemic therapies, TSEBT represented the mainstay of MF treatment, with conventional-dose TSEBT (cdTSEBT, 30-36 Gy) achieving long-term disease control in patients with early stage disease in the first-line setting. In current clinical practice, TSEBT is often deferred until later in the treatment paradigm, and frequently utilized to treat advanced, treatment-refractory disease, where the durability of disease control following TSEBT is uncertain. Earlier delivery of TSEBT in the treatment paradigm may benefit patients with MF For patients with MF refractory to topical chemotherapy and phototherapy, TSEBT withtranslational technique offers excellent local control (LC: CR+PR) and favorable OS rates along withsubstantial relief of symptoms.[11,12].

Conclusion

Skin directed therapies serve important roles in the treatment of early-stage MF, as well as managing symptoms and improving quality of life of all stages. For patient's refractory to topical chemotherapy and phototherapy, total skin electron beam therapy offers an excellent local control along with substantial relief of symptoms. Therefore, radiotherapy, including total skin electron beam therapy, continues to be a cornerstone of therapy for all stages of MF.

What is new?

Patients who fail to respond to one skin directed therapy (SDT), or who progress after an initial response like in this case report, may be treated with an alternative SDT. There is no evidence that development of resistance to one modality affects subsequent response to an alternative SDT In current clinical practice, total skin electron beam therapy (TSEBT) is often deferred until later in the treatment paradigm, and frequently utilized to treat advanced, treatment-refractory disease, where the durability of disease control following TSEBT is uncertain. Earlier delivery of TSEBT in the treatment paradigm may benefit patients with MF.

List of Abbreviations

EORTC	European Organization for Research and Treatment of Cancer
ISCL	International Society of Cutaneous Lymphoma
MF	Mycosis fungoides
nb UVB	Narrow band ultraviolet B
NCCN	National Comprehensive Cancer Network
PUVA	Psoralen plus ultraviolet A
RT	Radiotherapy
SDTs	Skin directed therapies
TSEBT	Total skin electron beam therapy

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this case report.

Funding

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Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval was obtained from the Institutional ethics boards.

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References

1. Duffy R, Jennings T, Kartan S, Song A, Shi W, Porcu P, et al. Special considerations in the treatment of mycosis fungoides. Am J Clin Dermatol. 2019;20(4):571–8. https://doi.org/10.1007/s40257-019-00431-z
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Primary Cutaneous Lymphomas Version 2.2020. 20202 April 10; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
3. Piotrowski T, Fundowicz M, Pawlaczyk M. Total skin electron beam therapy with rotary dual technique as palliative treatment for mycosis fungoides. *In Vivo*. 2018;32(3):517–22. https://doi.org/10.21873/invivo.11269
4. Smith GL, Wilson LD, Dabaja BS. Chapter 79 - mycosis fungoides. In: Gunderson LL, Tepper JE. Clinical radiation oncology. 4th ed. Philadelphia, PA: Elsevier; 2016. pp 1556–76. e4. https://doi.org/10.1016/B978-0-323-24098-7.00079-4
5. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, International Lymphoma Radiation Oncology Group. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2015;92(1):32–9. https://doi.org/10.1016/j.ijrobp.2015.01.008
6. Tarabadkar ES, Shinohara MM. Skin directed therapy in cutaneous T-Cell lymphoma. Front Oncol. 2019;9:260. https://doi.org/10.3389/fonc.2019.00260
7. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol. 2014;70(2):205.e1–222. https://doi.org/10.1016/j.jaad.2013.07.049
8. Hoppe RT, Advani R, Kim YH. 62 - Mycosis fungoides. In: Hoppe R, Phillips TL, Roach M, editors. Textbook of radiation oncology. 3rd ed. Philadelphia, PA: W.B. Saunders; 2010. pp 1380–93. Available from: http://www.sciencedirect.com/science/article/pii/B9781416058977000640; https://doi.org/10.1016/B978-1-4160-5897-7.00064-0
9. Chandra R, Kachnic L, Thomas Jr C. Contemporary topics in radiation medicine, Part II: disease sites, hematology/oncology clinics of North America. Amsterdam, Netherlands: Elsevier; Vol 34 (1), p 240, 2020. Available from: http://www.sciencedirect.com/science/article/pii/S088985881930142X; https://doi.org/10.1016/S0889-8588(19)30142-X
10. Hansen EK, Iii RM. Handbook of evidence-based radiation oncology. 3rd ed. Berlin, Germany: Springer; 2018. pp 761–72.
11. Campbell BA, Ryan G, McCormack C, Tangas E, Bressel M, Twigger R, et al. Lack of durable remission with conventional-dose total skin electron therapy for the management of sezary syndrome and multiply relapsed mycosis fungoides. Cancers (Basel). 2019;11(11):1758. https://doi.org/10.3390/cancers11111758
12. Gamsiz H, Beyzadeoglu M, Sager O, Dincoglan F, Uysal B, Demiral S, et al. Evaluation of mycosis fungoides management by total skin electron beam therapy with "translational technique". J BUON. 2015;20(4):1124–31.
13. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC) [published correction appears in Blood. 2008 May 1;111(9):4830]. Blood. 2007;110(6):1713–22. https://doi.org/10.1182/blood-2007-03-055749

Summary of the case

1	**Patient (gender, age)**	Male, 76-year old
2	**Final diagnosis**	Mycosis fungoides (MF)
3	**Symptoms**	Erythematous plaques dispersed through the trunk and lower limbs
4	**Medications**	None
5	**Clinical procedure**	Total skin electron beam therapy
6	**Specialty**	Radiation oncology