





Low-dose localised electron radiotherapy in a case of refractory mycosis fungoides

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We present a case of refractory mycosis fungoides (MF) that responded to low-dose localised electron radiotherapy. A 59-year-old man presented with a 5-year history of a generalised, pruritic, scaly, red skin rash that had recently become more nodular. Skin biopsy confirmed MF. After a variable initial response to topical steroids and oral methotrexate, progressive tumours were treated with low-dose electron radiotherapy. We describe the clinical effect of different radiation doses and fractionation schedules applied over a 2-year period. Our experience in this case of MF suggests that low-dose localised electron radiotherapy offers excellent palliation by effectively resolving tumorous lesions, improving quality of life and allowing for retreatment of refractory lesions.

Keywords: mycosis fungoides; electron radiotherapy; quality of life; cutaneous T-cell lymphoma; radiotherapy.

Introduction

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL) subtype. It is an extranodal, non-Hodgkin's lymphoma, first described in the literature in 1806. A recent Surveillance, Epidemiology and End Results (SEER) analysis demonstrated a dramatic increase in the incidence of MF from 3.0 per million person-years in the 1970s to 5.9 in the 2010s.¹ The reported incidence of MF is higher in men and in people of African descent.^{2,3,4}

Classically, MF manifests as flat patches or thin plaques on the skin and can progress to more substantive tumours as well as extracutaneous involvement. Patches or plaques may be localised or widespread. A definitive diagnosis of MF is often preceded by a 'premycotic' period ranging from months to decades, during which the patient may have nonspecific, slightly scaling skin lesions and nondiagnostic biopsies.⁵ These lesions may wax and wane over years, and a diagnosis of parapsoriasis or nonspecific dermatitis is often made in error. Mycosis fungoides is traditionally staged according to the MF Cooperative Group tumour-node-metastasis-blood (TNMB) classification of cutaneous T-cell lymphoma (CTCL) system which allocates stage according to the type of skin lesions (patch, plaque or tumours), percentage of total skin involved, nodal involvement and visceral and peripheral blood involvement.⁶

Survival outcomes relate directly to disease stage. Even though MF is regarded as a chronic condition, most patients with early-stage disease (St IA – IIA) will have a normal lifespan with management aimed at controlling the extent of disease, relieving symptoms and diagnosing and treating progression early. Patients with advanced disease (St IIB – IV), including Sezary syndrome, have reported 5-year overall survival (OS) rates of 28% – 68%, depending on the number of poor prognostic factors present.⁷ In addition to the poor risk factors described by the Cutaneous Lymphoma International Consortium (CLIC), namely St IV disease, age > 60 years and elevated lactate dehydrogenase (LDH), large-cell transformation in the skin and being of African descent have been independently associated with worse prognoses.^{3,4,7,8}

Treatment guidelines recommend skin-directed therapies (localised or generalised) as initial treatment in patients with early patch or plaque disease and the addition of milder systemic therapy for refractory, persistent or progressive disease whilst on skin-directed therapies.^{9,10}

Case

The patient, a previously well 59-year-old man, presented to the dermatology clinic in April 2019 with a 5-year history of a generalised, pruritic, scaly, red skin rash that had recently become more

nodular and was minimally responsive to over-the-counter topical steroid creams. A diagnosis of MF was confirmed on skin biopsy (CD3+, CD4+, CD20-, CD8-), with no evidence of large-cell transformation. At the time of diagnosis, the lesions consisted of patches, plaques and ulcerating tumours, mainly involving the skin of the thighs, groin and suprapubic region. The patient had no nodal or visceral involvement, and his peripheral blood smear was normal. He was staged as Stage IIB (T3N0M0B0).

The patient was started on topical clobetasol cream, emollients and oral methotrexate (MTX) at a low dose of 20 mg/week with folic acid supplementation, analgesics and anti-emetics. He was considered for ultraviolet-A therapy with psoralen (UVA therapy) but resided too far from the treating centre for this to be feasible. After four months, in September 2019, despite a partial response in some lesions, tumours on the left lateral thigh, right anterior thigh (Figure 1a) and left groin area did not improve on MTX therapy and continued to ulcerate.

Because of the refractory tumours, he was referred for radiotherapy (RT) to these areas for the first time in September 2019. The left lateral thigh, right anterior thigh and left groin were each treated to a total dose of 8 Gy each, delivered in two daily fractions using electron RT (Table 1). For this and all subsequent electron treatments, a normal tissue margin of 1.5 cm – 2 cm on clinical disease was delineated and the closest matching pre-cut electron insert was selected (rectangular or circular) (Table 1).

Due to the coronavirus disease 2019 (COVID-19) pandemic, the patient discontinued follow-up and MTX treatment for nine months during 2020. He presented again in January 2021, 16 months after his first course of RT, with a mixed picture of response and progression. The previously treated lesions on the left lateral thigh and right anterior thigh had resolved completely (Table 1), but the nodular left groin lesion showed only a partial response with central necrosis. A new fungating lesion had developed on the right medial thigh. A rebiopsy of a skin tumour showed no large-cell

transformation. Restaging computed tomography (CT) scan showed inguinal and iliac lymphadenopathy but no visceral involvement (T3N1M0B0, Stage IIIB). Methotrexate and topical therapy were restarted, and the two symptomatic areas were treated with single fraction electron RT of 8 Gy each (Table 1). The right groin plaque (Figure 1c) was noted to be more nodular but was not symptomatic at the time.

After four months on oral MTX, the patient reported improvement of plaques on the trunk and some of the previously irradiated lesions. The left groin lesion had reduced further after retreatment. The previously untreated right groin mass had increased in size and was oozing (Figure 1c). The right medial thigh lesions had initially responded to RT but were now enlarging again. A new fungating lesion had also developed on the left medial thigh (Figure 1b). Due to the fungating nature of the lesions and the apparent recurrence of the right medial thigh lesion, a planning CT scan was performed to determine the exact deep extent of each lesion. This enabled appropriate selection of electron energies to ensure coverage at depth. Electron RT to a total dose of 12 Gy, delivered in three daily treatments, was administered to the left medial thigh (Figure 1b) and to the right groin (Figure 1c) concurrently. The right anterior thigh lesion was retreated with 8 Gy in two daily fractions using electron RT (Table 1).

Within four months, the right groin lesion had ulcerated once again and was retreated with a single 8 Gy fraction. Two new ulcerating lesions on the right lateral and posterior thigh were treated to 12 Gy in three daily fractions of electron RT (Table 1).

At his last follow-up, all described lesions had regressed (Table 1, Figure 1a, b, c) and were asymptomatic.

Discussion

Mycosis fungoides accounts for about 50% – 70% of CTCL cases.¹¹ Significant prognostic factors for survival in patients with MF include age at presentation, extent and type of skin involvement, overall stage, presence of extracutaneous disease and peripheral blood involvement. Early-stage with limited patch or plaque disease has an excellent prognosis, whereas those with tumour-stage disease or erythrodermic skin involvement have a less favourable prognosis. Extracutaneous disease has a poor prognosis.¹²

In addition to topical pharmaceuticals, phototherapy and systemic agents, RT has been an effective modality used to control MF symptoms. Similar to normal lymphocytes, the neoplastic T-cells of MF are extremely radiosensitive with an estimated α/β ratio of more than 10.¹³ Total skin electron beam therapy (TSEBT) has been employed with high levels of efficacy and safety due to its wide treatment fields and superficial range of skin penetration.¹⁴ Total skin electron beam therapy is best employed in cases of diffuse but superficial skin involvement. However, many RT centres in sub-Saharan Africa, including the authors' own, do not have the capacity and necessary expertise to deliver this highly

TABLE 1: Sites of nodular lesions, dates treated (and retreated) and clinical response at 4 months post radiotherapy.

Site	Month treated				Clinical response at last follow-up (Feb 2022)
	Sep 2019	Jan 2021	May 2021	Oct 2021	
Left lateral thigh	8 Gy in 2#, 15 MeV	-	-	-	CCR
Right anterior thigh (A)	8 Gy in 2#, 15 MeV	-	8 Gy in 2#, 15 MeV	-	CCR
Left groin	8 Gy in 2#, 15 MeV	8 Gy in 1#, 12 MeV	-	-	CCR
Right medial thigh	-	8 Gy in 1#, 12 MeV	-	-	CCR
Right groin	-	-	12 Gy in 3#, 12 MeV	8 Gy in 1#, 12 MeV	CCR
Left medial thigh	-	-	12 Gy in 3#, 12 MeV	-	CCR
Right posterior thigh	-	-	-	12 Gy in 3#, 15 MeV	CCR
Right lateral thigh	-	-	-	12 Gy in 3#, 15 MeV	CCR

CCR, complete clinical response; MeV, megaelectron volt; Gy, gray.

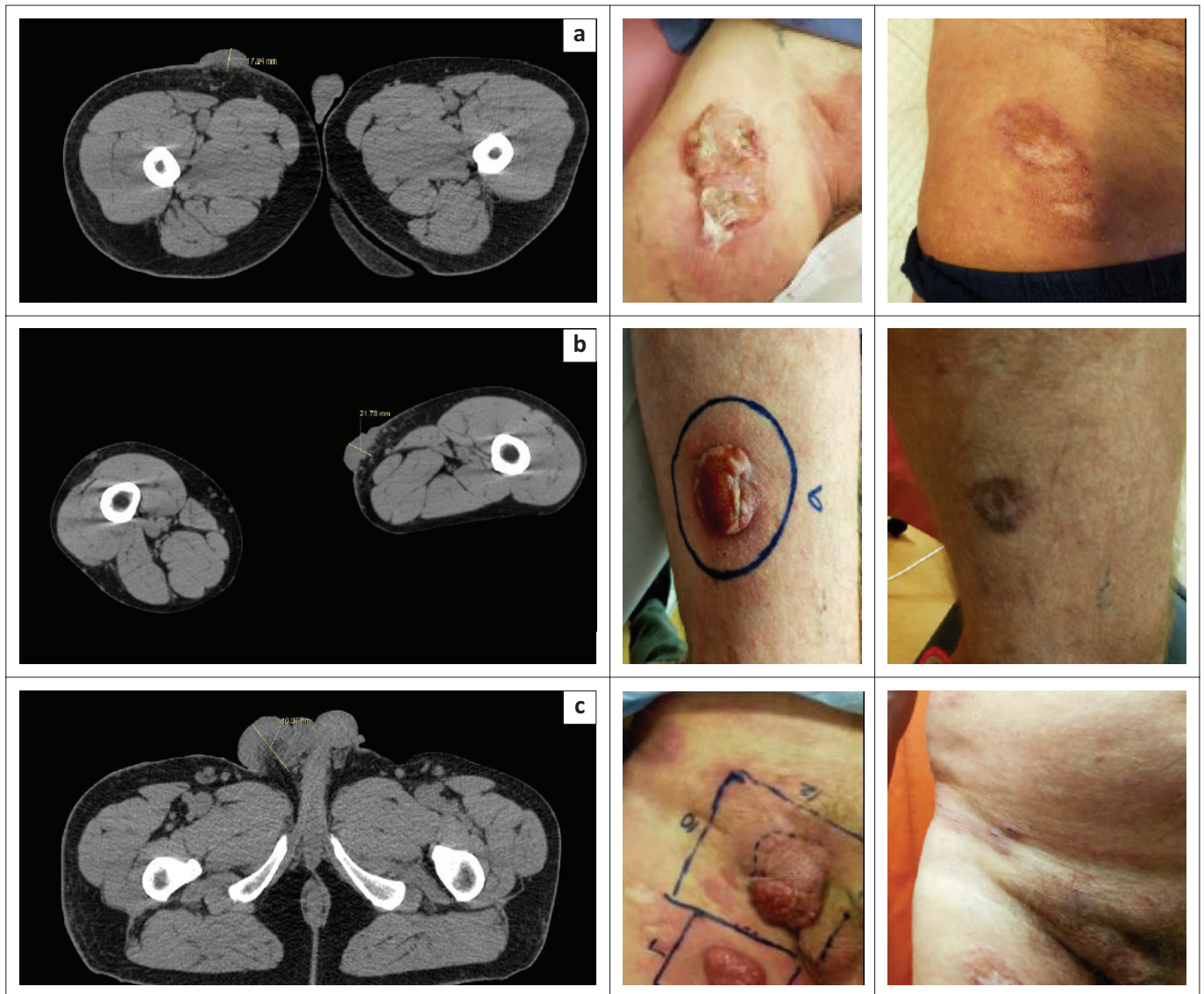


FIGURE 1: Computed tomography planning, preradiotherapy and postradiotherapy mycosis fungoides lesions (a) (right anterior thigh), (b) (medial left thigh), (c) (right groin).

specialised treatment modality. Disease response and relapse-free survival have been shown to be dose dependent, and traditionally doses of 30 Gy – 36 Gy were used for TSEBT. Extended follow-up has, however, demonstrated that relapses still occur at these dose levels and that long-term side effects like xerosis, alopecia and nail loss are significant.^{13,15} More recently, lower doses (10 Gy – 12 Gy) have been employed with the advantages of shorter treatment duration, fewer side effects and the opportunity for retreatment in the event of relapse.¹⁴ Such lower RT doses have allowed effective local palliation of cutaneous lesions with RT to doses ≥ 8 Gy.^{14,15,16,17} Total skin electron beam therapy was not indicated for this patient because of the thick and localised nature of his symptomatic lesions.

The evidence for localised palliative RT in the management of MF is scant. Early radiobiological evidence suggested that complete response could not be achieved at doses below 8 Gy and that fractionation over several days was feasible, as it had a protective effect on normal tissues whilst still achieving

tumour control.¹³ Small case series have reported complete response rates of 92% – 94% when using 8 Gy in 1 or 2 fractions.^{18,19}

Our patient received localised superficial electron RT to eight different MF skin sites over a period of 2 years. Apart from a 9-month period in 2020 when he discontinued systemic MTX therapy, his MF followed a waxing and waning course with an unpredictable pattern of varying progression and response in skin lesions. Electron RT to 8 Gy offered effective symptomatic relief for some lesions, but other areas required retreatment over the 2-year period. The patient received a total biologically effective dose (BED) of 36 Gy – 92 Gy to the skin and subcutaneous tissues of his pelvis and thigh area over a 2-year period.

Delivering a dose of 8 Gy – 12 Gy in 2–3 fractions appeared to induce longer remission periods than single fractions of 8 Gy. Although the patient did not report any pain, the discharge from the wounds posed significant challenges, such as soiling

of the clothes from constant serous discharge and foul smell, as well as secondary bacterial infection from breached skin.

CT planning is not routinely used for superficial RT to skin malignancies. The anatomy of the body site, pathophysiology of the disease and clinical findings are considered when determining target volumes. In the case of MF, disease originates in the epidermis, with dermal and subcutaneous infiltration only seen in thicker plaques and nodules. At the first treatment timepoint, electron energies were selected based on this knowledge. At the second treatment timepoint, however, it was considered prudent to use a CT planning scan to determine the depth of invasion of the large fungating lesion in the right groin as well as the recurrent lesion on the right medial thigh. There was some concern that the early recurrence could have been the result of underdosing the tumour at depth. CT planning was, however, only used during one of the four treatment timepoints in this patient, as it had showed that even with significant nodular fungation, subcutaneous invasion remained minimal. This knowledge informed future target definition and treatment selection.

Stage IIB MF is associated with a 5-year overall survival of approximately 56%.⁹ Despite the chronic nature of the disease and the significant impact that symptomatic MF lesions can have on a person's physical well-being, self-image, work and leisure activities and personal relationships, the impact of the various treatment modalities available for MF on quality of life is not well defined.²⁰ Our patient, a professional martial artist, described this treatment as an 'excellent and "lifesaving" intervention that has enabled me to live a near normal life'.

Conclusion

We observed complete response to most of the lesions treated with a fractionated dose range of 8 Gy – 12 Gy. Two lesions that initially showed a partial response to RT had a complete response following retreatment with 8 Gy in 2 fractions given over two consecutive days. The RT led to meaningful improvements in the patient's quality of life.

The use of low-dose total skin electron therapy has been widely recommended for the management of diffuse plaque-like MF. However, published guidelines on RT for isolated tumorous lesions in terms of dose, the number of fractions and the choice of electron energy rely on a limited evidence base.⁹ We hope that our account of successful low-dose focal electron RT treatment for isolated MF lesions offers oncologists, haematologists and dermatologists further options in the multidisciplinary management of this rare disease that may lead to improved quality of life for these patients.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

G.O.J., H.B., W.I.V. and Z.M. were involved in conceptualisation, design, writing and/or review and editing of the article.

Ethical considerations

Stellenbosch University Health Research Ethics Committee have been informed of the intention to publish (reference HREC: C22/02/001) the case report. Written informed consent was obtained from the patient.

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Data availability

The clinical data that support the findings of this case report are available from the corresponding author, G.O.J., upon reasonable request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of any affiliated agency of the authors.

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