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CASE REPORT

Treatment of Darier Disease with Radiation Therapy: Case Report and Literature Review

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Abstract: Darier's disease (DD) is an autosomal dominant genodermatosis characterized by hyperkeratotic papules, often accompanied by scaling and crusting. Managing DD presents significant challenges due to the absence of an effective cure, with only symptom targeting treatments currently available. This study presents a case of refractory DD that showed poor response to established pharmacological treatments but demonstrated improvement with low-dose superficial X-ray radiotherapy (SRT). The radiation was delivered as a single 200 cGy treatment, which visibly improved the condition. Considering the different degrees of side effects, sequelae, and risk of developing radiation-induced cancer after exposure to moderate levels of radiation, it may be considered that we attempt to treat recalcitrant DD initially by applying a low dose of radiation in order to mitigate these undesired side effects. If larger doses or additional courses are necessary due to inadequate response, the risks and benefits must be carefully evaluated and discussed with patients.

Keywords: Darier disease, superficial X-ray, low-dose of radiation, SRT-100

Introduction

Darier's disease (DD) is an autosomal dominant genodermatosis associated with a mutation in the *ATP2A2* gene. Histologically, acantholysis between suprabasal epidermal cells results in suprabasal clefting with papillomatosis and dyskeratosis. Electron microscopy reveals loss of desmosome connectors, and immunohistochemistry shows diffuse desmosome in acantholytic cells.[1] Primary lesions are small, densely keratinized red-brown papules with a grayish keratin plug, primarily found in seborrheic areas such as the forehead, nasolabial folds, neck, scalp, chest, back, and flexural regions including the armpits, groin, and submammary skin.[2] Management of DD presents challenges due to the lack of an effective cure, with only symptom targeting treatments available. Despite extensive investigation into various potential therapies, current treatment options remain largely unsatisfactory. We report a case of a refractory Darier patient who underwent superficial X-ray radiation therapy, achieving a favorable outcome, as described in the following sections.

Case Report

A 16-year-old male presented with red-brown hyperkeratotic papules primarily on the forehead, scalp, neck, chest, and underarms.

The histopathological examination (Figure 1) revealed acantholytic dyskeratotic cells in the upper epidermis, along with suprabasal clefts showing focal hyperkeratosis and parakeratosis. Clinical manifestations and histopathological features confirmed the diagnosis of DD. The patient underwent continuous treatment with topical steroids, adapalene gel, salicylic acid, tretinoin, urea, and oral retinoids, but responded poorly. Persistent itching and personal appearance concerns have placed a significant psychological burden on the patient. Therefore, we recommended low-dose superficial X-ray therapy. We utilized superficial X-ray radiotherapy (SXRT) with the FDA-approved SRT-100 apparatus (Sensus Healthcare, Boca Raton, FL, USA). Initially, treatment focused on the chest, administering a single dose of 200 cGy

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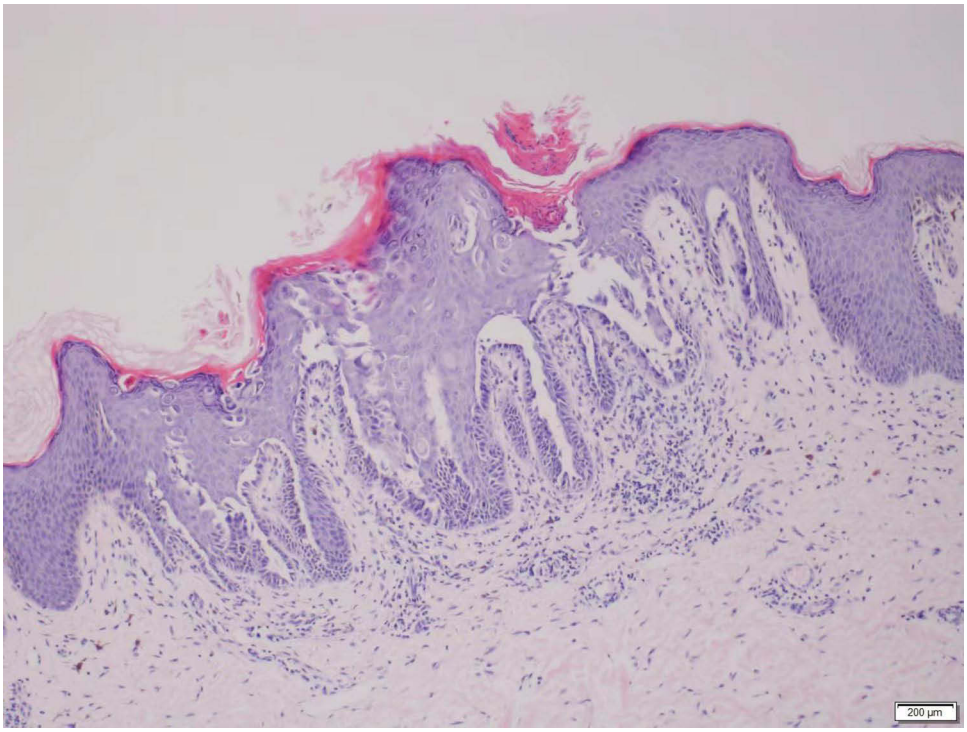

Figure 1 Histopathological examination revealed acantholytic dyskeratotic cells in the upper epidermis, suprabasal clefts with focal hyperkeratosis and parakeratosis.

using a 50KV tube voltage. Two months after treatment, significant improvement was observed in the chest lesions. Upon the patient's return to the clinic ten months later, chest skin lesions had nearly resolved, but lesions on the neck, underarms, and head had worsened. Given the lack of effective alternative treatments, the patient opted for superficial X-ray radiation therapy for the neck and underarms, choosing to avoid treatment for the head due to concerns about potential hair loss from radiation therapy. Additionally, to safeguard the thyroid gland, which is especially sensitive to radiation, we carefully delineated its margins using thyroid ultrasonography (Figure 2). The radiotherapy excluded the region between these margins (non-treatment target area). A single 200 cGy dose of radiotherapy was administered to the therapeutic target area on the neck and underarms. Four weeks after treatment, improvements were evident in the neck and underarm lesions, though some pigmentation remained. Interestingly, even the lesions in the non-treatment target

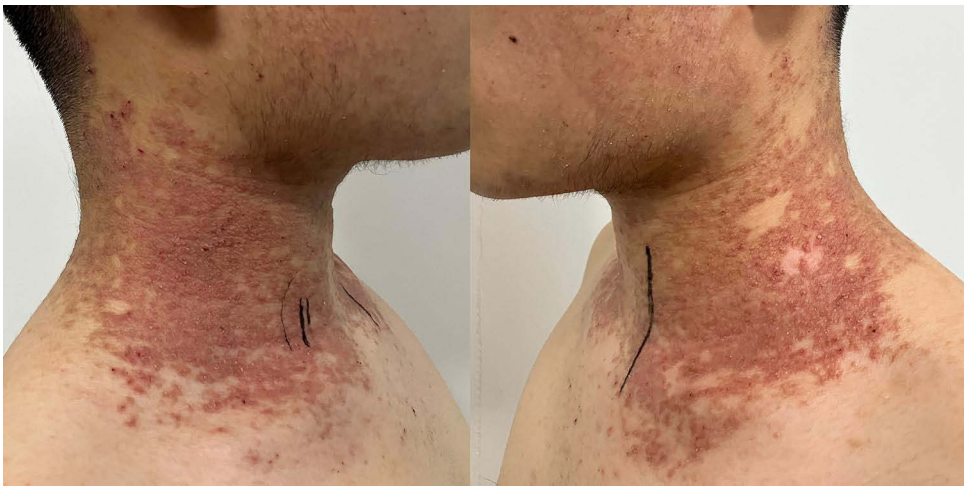

Figure 2 Before superficial X-ray radiation therapy.

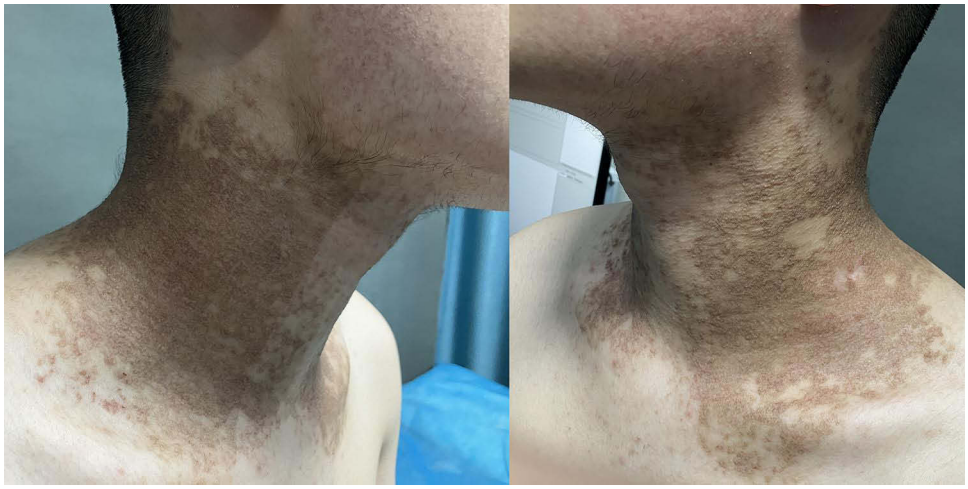

Figure 3 4 weeks after treatment, the skin lesions in the treatment area of the neck were obvious improved.

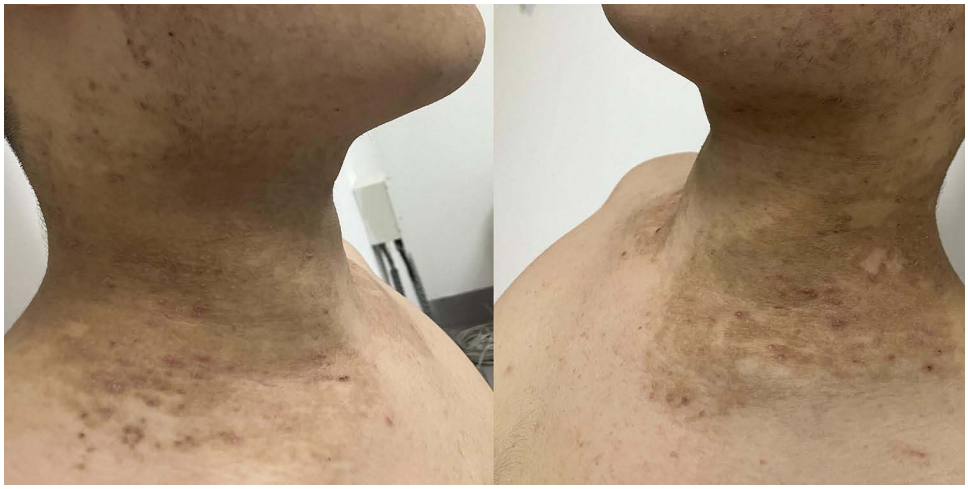

Figure 4 5 months after treatment, the skin lesions in the treatment area of the neck were virtually resolved.

area of the neck showed improvement (Figure 3). By five months after treatment, skin lesions on the neck and underarms had nearly resolved, and pigmentation had significantly improved (Figure 4).

Discussion

Currently, there is no definitive treatment for DD; management primarily focuses on avoiding triggers and controlling symptoms. This study reviews previous experiences with radiation treatment for DD. Table 1 outlines radiotherapy treatment parameters and treatment responses. From Table 1, it is evident that the majority of patients experienced either partial or complete regression of skin lesions or symptoms due to radiation therapy. Anthony Cipollaro et al[3] reported a case where DD lesions disappeared following radiation. Some areas improved after a single 150R X-ray irradiation, while others required two to three treatments. Kittridge et al[4] reported successful treatment of a female patient with DD using radiation. Initially, therapy targeted bilateral inframammary folds with a total dose of 2000 cGy in 10 fractions. However, the patient initially experienced severe localized dermatitis with moist desquamation at the treatment sites. Subsequently, the patient received total skin electron beam radiation (TSEB), but after only 900 cGy of TSEB, severe dermatitis, skin pain, nausea, and vomiting ensued, necessitating an extended hospital stay with intensive care unit admission. Leung et al[5] reported on three patients with severe refractory DD treated with photon and electron beam radiation therapy (RT), resulting in long-term remission of the treated area. However, one patient developed sclerosis and

Table 1 Treatment of DD with Radiation Therapy

Source	Site		Single Dose (Gy)	Fractions	Total Dose (Gy)	Complications	Results/Comments
Anthony[3]	Nil		1.5	Once or more	1.5 or multiples of 1.5	Nil	Complete regression
Kittridge[4]	Chest		2	10	20	Striae, mild flare, dermatitis	Complete remission
	Total skin		0.75	12	9	Dermatitis, skin pain, nausea, and vomiting	Complete remission
Leung[5]	Patient 1: Leg		Nil	Nil	30	Pain	Prolonged remission
	Patient 2: foot		Nil	Nil	30	Pain	Significant improvement
	Patient 3:	Chest	Nil	Nil	9	Nil	Response
		Right forearm	Nil	Nil	15	Nil	Response
		Left forearm, etc	Nil	Nil	19.5	Nil	Best response
		Pelvis, etc	Nil	16	40	Sclerosis and ulcerations	Significantly better control
Rodriguez[13]	Abdomen, neck		2	10	20	Nil	Great response
Cipollaro[14]	Upper back		0.75	6	4.5	Nil	Marked improvement
Wulf[15]	Nil		2	8	16	Inflammation	Complete clinical regression in 8; partial regression in 2

ulcerations on the back and neck after 4000 cGy treatment, with a treatment-resistant sacral ulcer. Additionally, Podgornii et al[6] and Mac Manus et al[7] independently documented cases of DD showing marked clinical improvement due to cancer radiotherapy. Compared to other studies, we employed very low radiotherapy dosages and achieved significant clinical efficacy with no observed adverse effects or sequelae apart from pigmentation. Although there was significant improvement in the non-treatment target area of the neck without radiotherapy, we did not attribute this solely to natural disease progression due to lack of changes in other areas of the body that did not receive radiation therapy, such as the head and forehead. This unexpected result may be related to a reverse Koebner phenomenon occurring in this area.[8] Despite the unclear mechanism of action, various radiation techniques such as Grenz Ray, electron beam radiation, and conventional X-ray therapy have been employed for the treatment of benign dermatoses, including DD, with varying degrees of success. In the 1990s, literature reported the use of low-dose radiotherapy for drug-resistant psoriasis, chronic lichen simplex, eczema, and other pruritic diseases. The recommended treatment regimen consists of a single dose of 50–100 cGy once a week for 3–4 weeks, with a total dose of 200–400 cGy.[9] The significant therapeutic effects demonstrate the effectiveness of low-dose superficial X-ray radiotherapy for DD, although the process by which radiotherapy influences DD is unknown.[10] This extremely low radiation dose offers a new option for DD radiotherapy and causes minimal side effects, which is beneficial to patients. Therefore, the optimal dose and parameters of radiotherapy for DD remain unknown, but the minimal dose necessary to remove skin lesions should be employed, as the potential for side effects is significant. Considering the significant potential side effects, sequelae, and especially the risk of developing radiation-induced cancer after exposure to moderate levels of radiation,[11,12] it is advisable to initially administer local low-dose radiotherapy when using radiotherapy for DD. If larger doses and additional courses are required due to poor response, the risks and benefits need to be thoroughly evaluated and discussed with patients.

Conclusion

Radiation therapy may be considered as a potential treatment option for severe and refractory DD patients. However, there is no consensus on the optimal therapeutic protocol. Dermatologists may be considered using low-dose radiation for DD that does not respond to standard treatments.

Data Sharing Statement

Data would be available upon requests to corresponding author.

Consent Statement

Written informed consent for publication of their details and accompanying images was obtained from the patient's parent. A copy of the consent form is available upon request. Institutional approval was not required to publish the case details.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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