

Long-term improvement of recalcitrant Darier disease with photon and electron beam radiation therapy



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INTRODUCTION

Darier disease (DD) is a dominantly inherited genodermatosis that initially presents as small, firm, and greasy skin-colored or yellow-brown papules affecting seborrheic areas. These lesions are associated with hyperkeratosis, darkening, scaling, and maceration. Although cases of mild to moderate DD are rarely life threatening, severe recalcitrant DD that results in multidrug-resistant infections and requires frequent hospitalizations can be life threatening. Although many modalities of treatment have been investigated, treatment options to date are largely unsatisfactory. We describe 3 cases of severe recalcitrant DD treated with photon and electron beam radiotherapy (RT) that resulted in long-term remission of treated areas.

CASE REPORTS

Patient 1, a 37-year old woman, presented with thick, extremely painful and friable keratotic papules on her right lower extremity. Shave biopsy found acantholytic dyskeratosis consistent with the linear variant of DD. The skin eruptions first appeared at 20 years of age, starting on the right foot, then spreading up her right leg to her trunk. It was refractory to topical steroids, 5-fluorouracil, Silvadene cream, and salicylic acid. Isotretinoin resulted in mild improvement but with intolerable side effects even at a low dose. Patient 2, a man in his 40s, diagnosed at age 28, presented with hyperkeratotic lesions with significant drainage on the dorsum of his bilateral feet. He had hyperpigmented macules and thin plaques on the palms and

Abbreviations used:

DD: Darier disease
 RT: radiotherapy

hyperkeratotic papules on the neck folds. Biopsies of neck and hands showed hyperparakeratotic plugs and epidermal acantholysis, consistent with DD. Family history was positive; his mother had symptoms on her scalp and hands. Patient 2 did not respond to topical steroids, salicylic acid, tretinoin, urea, and oral retinoids (Fig 1, A). Recalcitrant disease and thickened hyperkeratotic contours in both patient 1 and 2 led us to use photon instead of electron beam therapy to penetrate more deeply. Each received a total dose of 30 Gy at 6 MV photons. Within 1 week, patient 1 exhibited a significant decrease in pain and size of the plaques as exophytic hyperkeratosis fell off. Skin color, texture, and turgor underlying previously treated lesions were normal. Pain from RT resolved completely after 2 months. She has not required a second course of RT. Patient 2, who had previously been unable to ambulate, was able to ambulate after his first course of treatment. After experiencing significant improvement with RT, he underwent a second course of treatment 1 year, 7 months later, this time including his palms. He now has significantly less pain on ambulation and has been able to exercise (Fig 1, B).

Patient 3 is a man in his 50s who presented with increasingly numerous, severe, painful, and hyperkeratotic papules and crusted, fissured plaques on his

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Fig 1. Patient 2. A 42 year-old man with consistent histology and positive family history of DD presents with thickened, hyperkeratotic papules and plaques on plantar right foot, palms, and neck folds, associated with significant pain and drainage that had been recalcitrant to multiple treatments: **A**, Before photon radiation therapy. **B**, After second course of photon radiation therapy.

head, neck, submammary folds, axillae, arms, popliteal, back, and groin. Symptoms were functionally limiting, and simple tasks like putting on clothing was painful. He was previously followed up by dermatologists at another academic institution with reported biopsies consistent with DD. V-shaped nicking of fingernails with bands and a family and personal neuropsychiatric history supported this diagnosis. He had been treated with hydroxychloroquine, mycophenolate mofetil, isotretinoin, 5-fluorouracil, and acitretin with incomplete control, resulting in frequent hospitalizations for methicillin-resistant *Staphylococcus aureus* and herpes simplex virus superinfections. We started RT on areas that were most painful and functionally limiting. A total of 6 MeV electrons was initially given

to 3 anatomically favorable sites: right chest wall, 9 Gy; right forearm, 15 Gy; and left forearm, 19.5 Gy. The 19.5-Gy dose resulted in the best response, so subsequent treatments were performed on the knees and antecubital area. The patient tolerated the dose well. Treatment was applied to more difficult areas including the anterior pelvis, flank, and groin, shielding and sparing the penis. Because of a good initial response, we ultimately increased the dose to a maximum dose of 40 Gy in 16 fractions. A total of 14 courses over the span of 6 years resulted in significantly better control with reduced frequency of hospitalizations and secondary infections. He is, however, being treated for sclerosis and ulcerations on the treated sites of his lower back and posterior neck, likely because of aggressive radiation therapy.

DISCUSSION

DD involves a genetic defect of an ATPase sarcoplasmic/endoplasmic reticulum calcium pump, the mutation of which causes the loss of desmosomal adherence seen in DD,^{1,2} Several clinical variants of DD include unilateral, localized, segmental, and acral. Despite much progress in understanding the underlying abnormalities of DD, treatment is unsatisfactory. Common dose-related side effects of retinoids can become so troublesome that patients prefer to live with their disease.³ A few reports have found doxycycline,⁴ fractional CO₂ laser,⁵ 5-fluorouracil,⁶ tacrolimus,⁷ and photodynamic therapy⁸ to be effective. To the best of our knowledge, radiation therapy has been used only in 3 published reports, 2 of which presented inadvertent improvement of DD during cancer RT.⁹⁻¹¹ Our cases are novel in that we used radiation therapy to treat DD and were able to demonstrate sustained results spanning years with our approach. The acute and temporary adverse effects of RT included fatigue, pain, transient erythema, and itching of irradiated sites. Because radiation is linked to oncogenesis, we recommend that for milder cases of DD, radiation should be the last resort, especially for younger patients, given the long latency of radiation-induced malignancy. Furthermore, chronic radiation dermatitis can occur in patients who require more courses of RT. Patient 3, who was re-irradiated to the sacral area, subsequently had a sacral ulcer that was challenging to heal. In patients who require re-irradiation, risks and benefits should be weighed. During the follow-up periods of our patients, new lesions developed in untreated body sites, while the irradiated areas remained largely quiescent. The 3 patients experienced reduction in pain and size associated with lesions and improved function.

CONCLUSION

Photon and electron RT provide a beneficial local effect through prolonged remission and is an effective option for patients with severe recalcitrant

DD. Patients who require re-irradiation may be at a higher risk for ulcerations and long-term risk of malignancy.

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