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Fractional epidermal grafting in combination with laser therapy as a novel approach in treating radiation dermatitis

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Abstract

Radiation injury to the skin is a major source of dysfunction, disfigurement, and complications for thousands of patients undergoing adjunctive treatment for internal cancers. Despite the great potential for affecting quality of life, radiation injury has received little attention from dermatologists and is primarily being managed by radiation oncologists. During our volunteer work in Vietnam, we encountered numerous children with significant scarring and depigmentation of skin from the outdated use of radioactive phosphorus P32 in the treatment of hemangiomas. This dangerous practice has left thousands of children with significant fibrosis and disfigurement. Currently, there is no treatment for radiation dermatitis. Here, we report a case series using the combination of laser treatment, including pulsed-dye laser, fractional CO_2 laser, and epidermal grafting to improve the appearance and function of the radiation scars in these young patients. We hope that by improving the appearance and function of these scars, we can improve the quality of life for these young patients and potentially open up a new avenue of treatment for cancer patients affected with chronic radiation dermatitis, potentially improving their range of motion, cosmesis, and reducing their risk of secondary skin malignancies.

Radiation injury to the skin is a major source of dysfunction, disfigurement, and complications for thousands of patients undergoing adjunctive treatment for internal cancers.[1] The risk, severity, and nature of radiation-induced fibrosis late effects depend on several factors including treatment-related factors (radiotherapy, surgery, and chemotherapy), patient-related factors (physiological status and age), comorbidity factors, particularly cardiovascular disease, preexisting collagen vascular diseases, and hypersensitivity or very rare congenital diseases.[2] Despite the great potential for affecting quality of life, radiation injury has received little attention from dermatologists and is primarily being managed by radiation oncologists. The lack of multidisciplinary cross-talk means that many doctors who directly see these patients are unaware of the potential treatment options. During our volunteer work in Vietnam, we encountered numerous children with significant scarring and depigmentation of skin from the outdated use of radioactive phosphorus P32 in the treatment of hemangiomas. This dangerous practice has left thousands of children with significant fibrosis and disfigurement. Currently, there is no treatment for radiation dermatitis. Here, we report a case series using the combination of laser treatment including pulsed-dye laser, fractional CO_2 laser, and epidermal grafting to improve the appearance and function of the radiation scars in these young patients. We hope that by improving the appearance of scars, we can improve the quality of life for these young patients as well as cancer patients who otherwise would go through life with a disfiguring defect, not to mention pain and limitation of motion,[3] and increased risk of secondary skin malignancies.[4-6]

Background

Radiotherapy, an essential modality in cancer treatment, frequently induces a fibrotic process in the skin which can lead to increased risk of malignancy,[4-6] poor wound healing,3 pain and limitation of movement,[3] and permanent loss of skin appendages with hyper- and hypopigmentation, decreased sweating and xerosis, all posing significant cosmetic and quality of life issues.[1] Long thought to be irreversible, radiation induced fibrosis (RIF) is now believed to be a dynamic process, characterized by constant remodeling and long-term abnormal fibroblast activation as well as dysregulation of the normal wound healing process.[7] Abnormal keratinocytes also participate in this abnormal feed-back loop, contributing to a "perpetual wound."8 Radioactive phosphorus P32 has been used in Vietnam since the 1970s for the treatment of hemangiomas. The children would go to the Cancer Hospital in Ho Chi Minh City to get biweekly treatments of radioactive P32 paste on their hemangiomas for up to 18 months. The result is fibrotic skin with severe scarring, depigmentation, loss of adnexal structure, and telangiectasias. Biopsies obtained from children with P32-induced dermatitis show either chronic- or late-radiation changes with features of morphea, dermal collagen sclerosis, vascular ectasia, loss of adnexal appendages, radiation fibroblasts, epidermal atypia, hyperkeratosis, and some thickening of upper dermal microvessels (Figure 1). Other biopsies show skin with lichen simplex chronicus-like changes with hypergranulosis, acanthosis, spongiosis, perivascular lymphocytic infiltrate, and ectatic papillary dermal vessels with thrombi (Figure 1). Fibrosis in the dermis after radiation is similar in many ways to other fibrotic lesions such as burn scars and localized scleroderma. Recent advances in laser therapy have paved the way for the use of fractional laser treatment in normalizing these scars, though this technique particularly has not been studied for radiation injury. Given that a significant number of radiation dermatitis scars also involve telangiectasias, pulsed-dye lasers (PDL) have been used to reduce the erythema factor.[9] Based on the characteristics of the radiation scars from these biopsies, we hypothesized that therapies that can modulate the fibrosis as well as reduce telangiectasias, and may be helpful in reversing these chronic changes. Particularly, the use of PDL and fractional laser treatments (FLT) can help improve the appearance and function of a radiation scar. In addition, skin affected by radiation dermatitis can have significant epidermal damages that can lead to precancerous lesions and skin cancers, especially with topically applied agents such as radioactive phosphorus P32. Replacing the epidermis may have the potential to significantly reduce the occurrence of future malignancies in these patients.

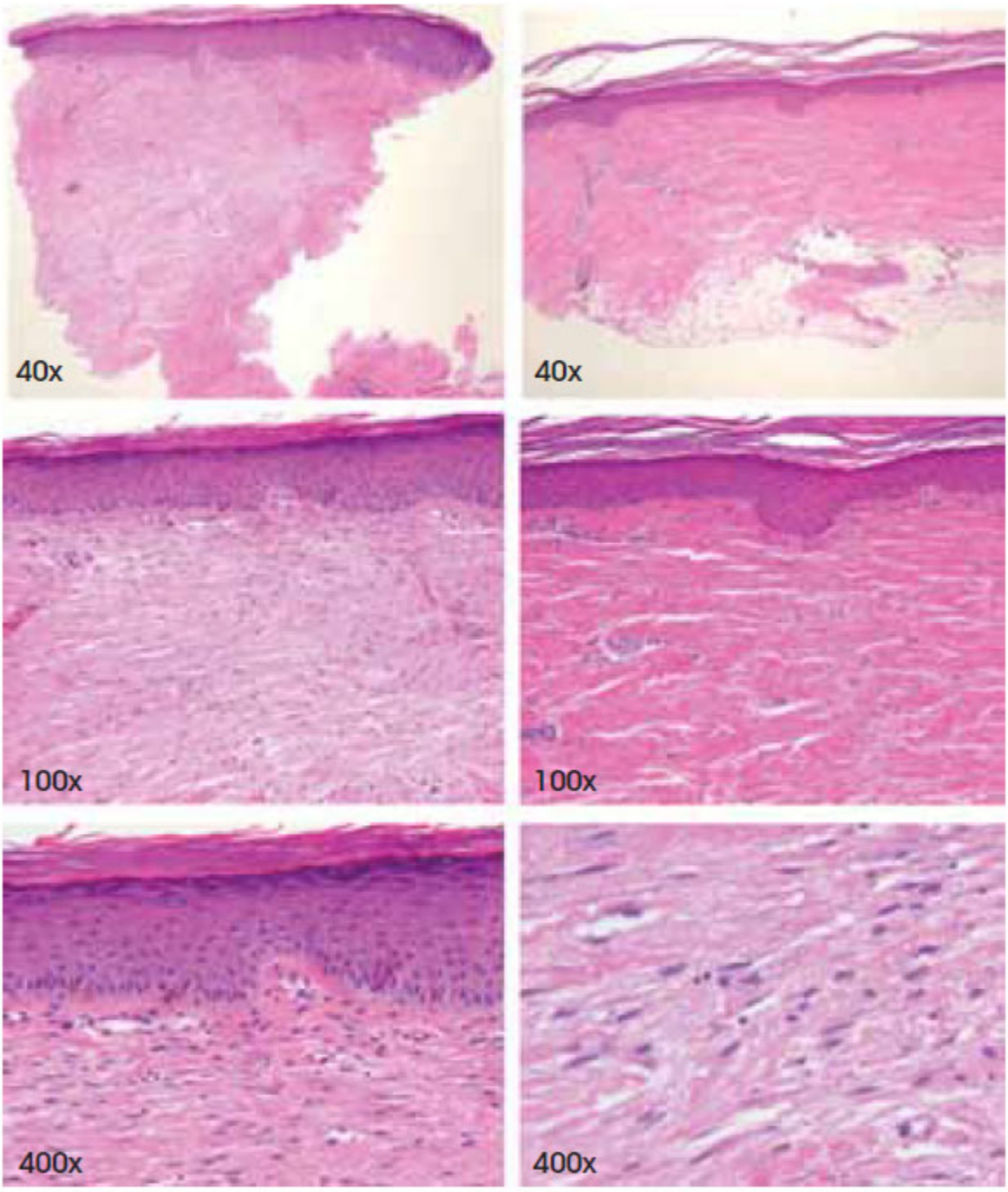

Figure 1. Pathology of radiation dermatitis from P32. Biopsies show chronic or late radiation changes with features of morphea, dermal collagen sclerosis, vascular ectasia, loss of adnexal appendages, radiation fibroblasts, epidermal atypia, hyperkeratosis, and some thickening of upper dermal microvessels. Other biopsies show skin with lichen simplex chronicus-like changes with hypergranulosis, acanthosis, spongiosis, perivascular lymphocytic infiltrate and ectatic papillary dermal vessels with thrombi (these vessels are reminiscent of angiokeratoma-type vessels.

Increasingly, pulsed-dye and fractional CO_2 lasers are used to modulate the symptoms, function, and cosmesis of the hypertrophic scar.[10,11] A recent large prospective cohort study found that the two combined laser therapies dramatically improved both the signs and symptoms of hypertrophic burn scars, as measured by objective and subjective instruments, when using the PDL for pruritus and erythema and the fractional CO_2 laser for stiffness and abnormal texture.[12] Over the past decade, multiple studies have demonstrated the effective use of PDL in providing significant and long-term improvement in hypertrophic scars.[13-17] Advances in laser therapy have led to the use of FLT to treat fibrosis associated with hypertrophic scars[12,18-20] and morphea,[21] leading to tissue repair, scar remodeling,[22-27] and relaxation of scar contractures.[28,29] Although the fractional CO_2 laser (10600 nm) is relatively new, the fractional concept has been applied to other wavelengths, such as the erbium-doped YAG laser crystals (Er:YAG; 2950 nm). A recent case report noted improvement in atrophy, contracture, texture, and color of a burn scar on the chest after two treatments with the fractional CO_2 laser.[39] The laser's safety and efficacy in comparison to dermabrasion was recently confirmed in a trial of 60 patients.[40] It is theorized that the reason the CO_2 laser has proven to be superior to lasers that utilize other wavelengths is because it normalizes growth factors in wound healing.[41] There have been recent reports outlining the effectiveness of PDL on keloidal and hypertrophic scars.[13,42] It has been proposed that PDL can down-regulate TGF-1 expression and up-regulate matrix metalloproteinase 13 (MMP-13) activity, as well as increase fibroblast proliferation and collagen type III deposition, resulting in keloidal scar regression.[43,44] Therefore, PDL may be a useful tool to improve radiation scars both in cosmesis and the fibrotic response. Recently, FLT has also been shown to decrease the occurrence of senescent fibroblasts in geriatric dermis, increase the dermal expression of insulin-like growth factor-1 (IGF-1), and correct the abnormal UVB response observed in untreated geriatric skin.[30] By creating zones of ablation at variable depths of the skin, the fractional laser has been shown to normalize dermal collagen and modulate TGF-β1 expression, likely through the coordinated expression of heat shock proteins and other factors, such as matrix metalloproteinases (MMPs) with the subsequent induction of a wound healing and collagen remodeling response.[31] These ablative zones may also serve as portals to enhance delivery of drugs and other substances.[32,33]

Blister grafting, a valuable method for epidermal placement, has been widely used in the treatment of vitiligo by replacing the depigmented epidermis with suction grafts from the normal skin area.[34-37] However, large blister grafts are difficult to handle and the larger graft area takes longer to heal. Minigrafting is a technique developed from hair transplantation techniques in which fullthickness punch grafts from normal pigmented skin are grafted to depigmented areas. It typically results in rapid and complete repigmentation in a high percentage of subjects. During classic minigrafting procedures, both donor and recipient areas are prepared using the same punch technique. A number of holes in the recipient area are inserted into the upper dermis. The same number of holes in the donor area are extracted and placed in the recipient holes. Minigrafting or full-thickness punch grafts result in repigmentation. However, a "cobblestoning appearance" in the recipient site is a potential adverse effect of this method, which is not acceptable to most patients. In contrast, cobblestoning does not occur when only the epidermis is grafted. The fractional epidermal micrografting technology was recently developed at the Wellman Center for Photomedicine (Boston, Massachusetts, USA) and licensed to MoMelan

Technologies for commercial development (Cambridge, MA).[38] In this strategy, a 25-cm^2 array of 100 small blisters was raised, simultaneously harvested, and captured directly onto an adhesive dressing (Tegaderm, 3M Company, St Paul, Minnesota, USA). This dressing with the micrografts was then transferred to the prepared recipient site, thereby repopulating the epidermis. In this case series, we evaluated whether PDL and/or FLT can help improve radiation-induced fibrosis and induce normal scar remodeling and whether replacing the damaged epidermis with fractional blister grafting will improve the epidermal barrier function and restore normal keratinocyte function. Understanding and correcting this underlying fibrotic process can help restore normal skin functions in patients affected with chronic radiation dermatitis and other debilitating fibrotic diseases in dermatology such as scleroderma, morphea, or nephrogenic systemic fibrosis.

Material and methods

In this case series, we treated 3 patients with either PDL followed by FLT, PDL alone, or FLT alone depending on the nature of the radiation scars. All patients received epidermal grafts on a portion of their scars after the laser treatment. A 595-nm PDL (V-beam Perfecta, Candela Corp, Wayland, MA) with a dynamic cooling device (DCD) was utilized for all treatments. This device is cleared by the US Food and Drug Administration (FDA) for clinical treatment of vascular lesions. Protective eyewear for the patient and all participants in the treatment room was provided. A spot size of 7 mm or 10 mm was used with an average fluence (energy delivered per unit area, in J/cm^2) of 7-9 J/cm^2. Fluence will vary according to patient and telangiectasias characteristics, including age, skin type, location, size of the vessels, and response to treatment. A 30-50 ms cryogen spray cooling (CSC) duration preceded the laser pulse duration of 0.4-1 ms. Each PDL treatment (up to 2 passes) lasted no longer than 10 minutes each. Treatment was performed with a spot overlap of ~20% as needed to achieve even coverage of the entire lesion.

The UltraPulse Encore CO_2 laser (Lumenis, Yokneam, Israel) was used for fractional laser treatment using the Deep FX handpiece. Very low density FLT (5%-10%) and pulse energy (20-50 mJ) was used to stimulate remodeling. The Active FX handpiece was used to remove the epidermis at higher density (50%) and low energy (10-15 mJ). Appropriate wound care instruction and follow-up was given to all patients. The Active FX handpiece of the UltraPulse laser produces relatively broader superficial columns of ablation and dermal heating and was used to prepare the recipient site for epidermal grafting. The Deep FX handpiece produces deeper, narrower columns of ablation and dermal heating. This theoretically allows the operator to customize treatment parameters based on scar size, thickness and desired outcome (ie, deeper/narrower for improved fibrosis, broader/superficial for improved cosmesis, and epidermal removal).

Finally, we also evaluated the use of an epidermal blister grafting technology, using a harvesting and grafting process designed by MoMelan Technologies (Cambridge, MA).[38] The overall concept is to harvest an array of many small epidermal blisters from a normal skin area (such as the thigh) using the Cellutome device (now Kinetic Concepts, Inc or KCI; San Antonio, Texas, USA), that adheres the micrografts of normal skin to a sterile wound dressing (Tegaderm, 3M Company, St. Paul, MN). The recipient skin site is prepared by removing its epidermis,

which we performed under local anesthesia with 1% intradermal lidocaine with epinephrine, using a CO_2 Laser (Ultrapulse; Lumenis, Yakum, Israel) delivering 10-14 J/cm^2 fluence in a single pass. After removal of the epidermis from radiation-exposed skin, the array of epidermal blisters is applied, using the epidermis-carrying Tegaderm dressing. A bolster dressing and tape were then applied, to ensure good contact of the epidermal blister array with the skin. This system combines the advantages of blister generation and minigrafting procedures. Both blister generation and the laser resurfacing procedures only removed the epidermis and did not breach the dermis. Blister generation is painless and did not require any anesthesia. The donor site for these patients was the thigh, and healing was completed within a week without scarring.

Results

Patient 1 was treated with Deep FX fractional CO_2 treatment followed by epidermal blister grafting. Prior to the fractional treatment, the patient had significant fibrosis of her skin, skin hardening, and depigmentation. Given the amount of depigmentation, we chose to do the blister grafting procedure after fractional laser treatment to see whether we could restore her epidermis. The procedure was repeated a year later (Figure 2). Patient 2 had significant telangiectasias and depigmentation on her temple after radioactive P32 treatment but less fibrosis of the dermis. We chose to give her 3 PDL treatments prior to epidermal grafting (Figure 3). Patient 3 had significant fibrosis of the skin as well as depigmentation. She was treated with the Deep FX fractional CO_2 laser and epidermal grafting, followed by one or more fractional CO_2 treatment (Figure 4). Patients 1 and 3 both had skin hardening and depigmentation with radioactive phosphorus treatment, while Patient 2 had mostly depigmentation and telangiectasias. We used FLT at a very low fluence and density for Patients 1 and 3 followed by epidermal grafting. In both of these patients, softening of the skin was noticed and patients reported more flexibility of the skin in the area treated with the fractional laser. Both patients had significant repigmentation of the skin after epidermal grafting and the skin surface was soft and smooth, resembling normal skin. However, we also noticed that the surfaces of the skin after FLT, despite softening and improvement in texture, also retained tiny pixelated indentations that corresponded to the fractional laser columns of ablation 3 months after treatment. We also observed that the pixelated indentations are no longer visible after two years. While we do not have biopsy results to evaluate whether these are tiny scars, it is clear that post-radiation may not heal normally after FLT. Patient 2 was treated with a PDL three times prior to epidermal grafting. Her telangiectasias were clearly improved by the PDL. Epidermal grafting only partially improved the depigmented area (Figure 3). One of the difficulties in epidermal grafting is to ensure the adherence of the micrografts to the prepared wound beds. Concave surfaces are much harder to ensure tight compression after epidermal transfer than convex surfaces. Location also makes a big difference, with facial location being more difficult for a graft transfer and adherence than the extremities or the trunk. The area affected by radiation dermatitis also showed softening and improvement in texture after PDL treatment.

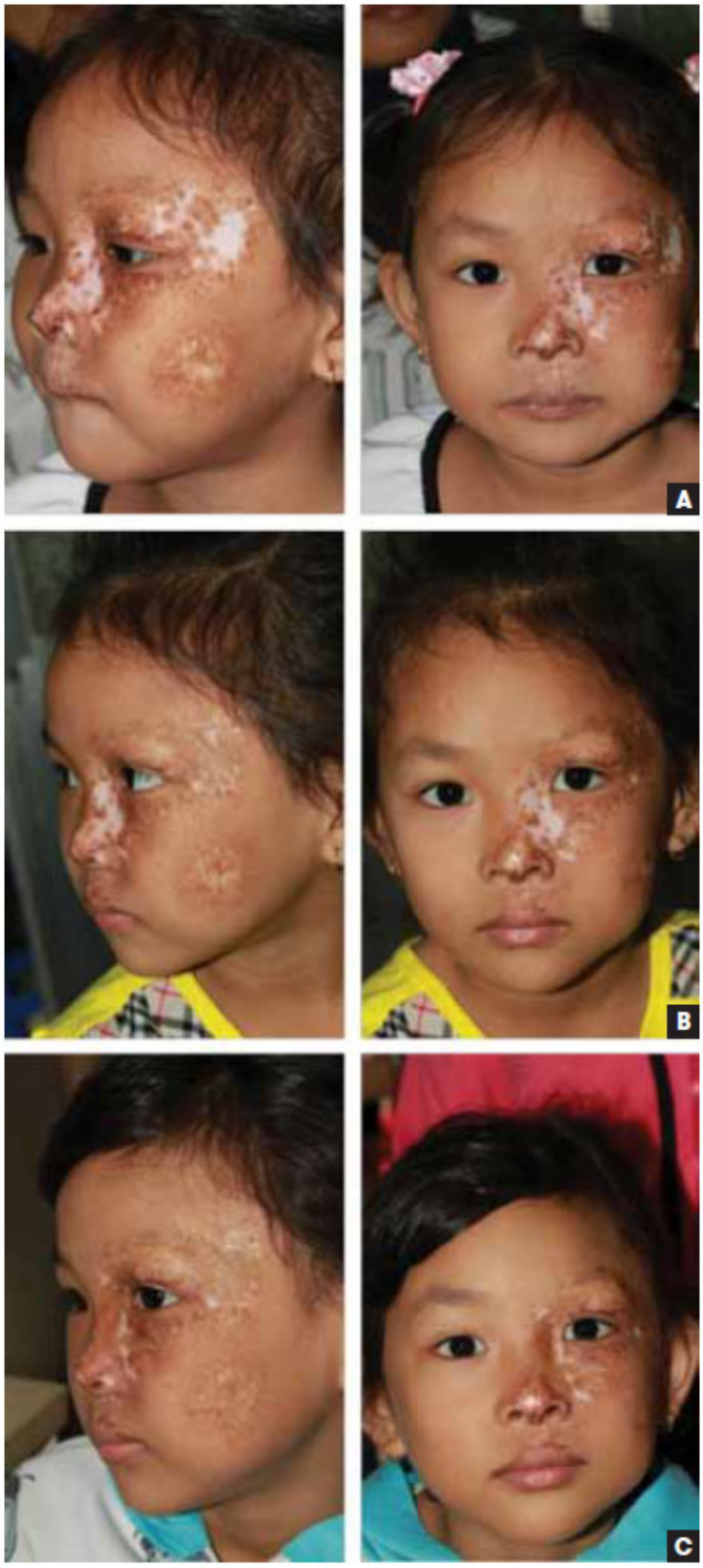

Figure 2. A) Patient 1 before treatment, B) after first fractional laser and epidermal grafting, and C) after second fractional laser and epidermal grafting procedure.

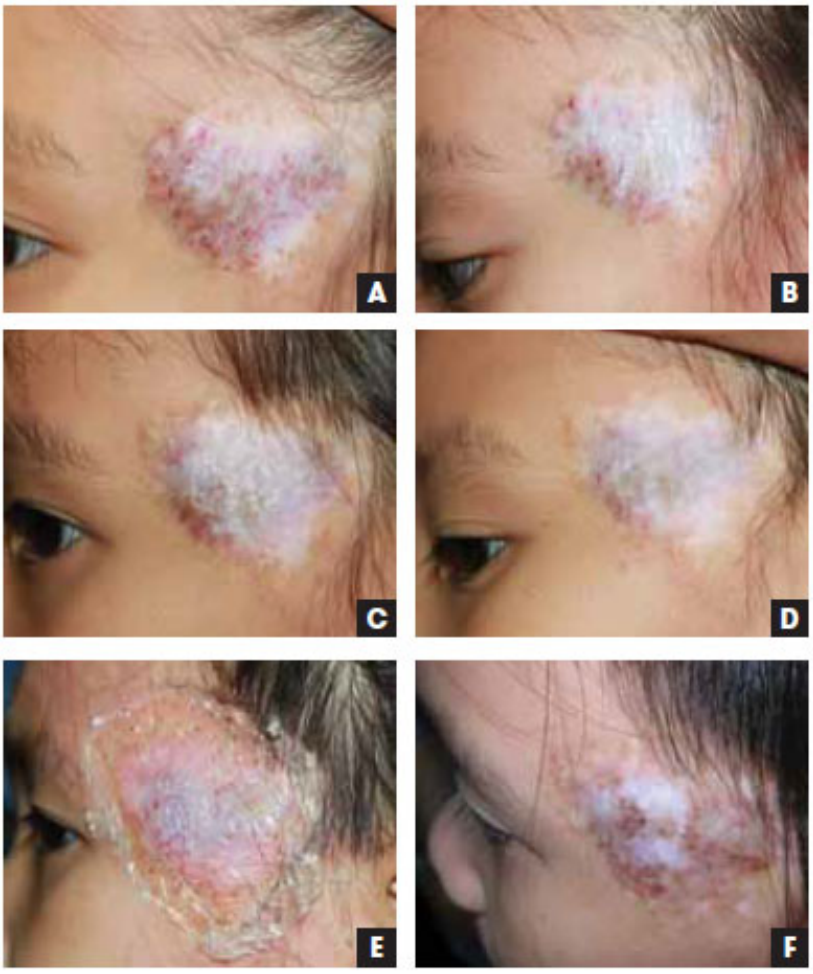

Figure 3. A) Patient 2 before treatment, B) after first PDL, C) second PDL, D) third PDL, E) epidermal graft: immediately after procedure, and F) 3 months after procedure.

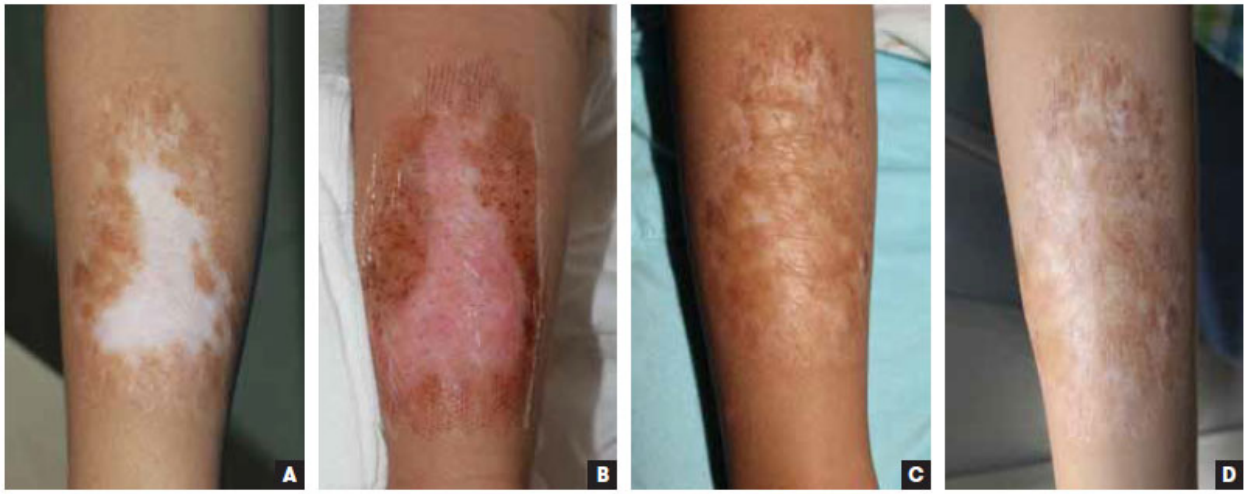

Figure 4. A) Patient 3 before treatment, B) after fractional CO_2 and epidermal grafting: immediately after procedure, C) 3 months after procedure, and D) after second fractional CO_2.

Discussion

Radiation fibrosis and dermatitis is a permanent and disfiguring outcome of many life-saving radiation procedures. In addition, outdated procedures such as the use of radioactive phosphorus P32 in the treatment of childhood hemangiomas poses significant scarring and depigmentation on many young children in developing countries such as Vietnam. There is a range of skin reaction to radioactive phosphorus as well as radiation treatment. Biopsies obtained from children with P32-induced dermatitis show chronic- or late-radiation changes with features of morphea, dermal collagen sclerosis, vascular ectasia, loss of adnexal appendages, radiation fibroblasts, epidermal atypia, hyperkeratosis, and some thickening of upper dermal microvessels. Other biopsies show skin with lichen simplex chronicus-like changes with hypergranulosis, acanthosis, spongiosis, perivascular lymphocytic infiltrate, and ectatic papillary dermal vessels with thrombi. In the appropriate clinical context, the histological findings are consistent with late radiation dermatitis with scleroderma/morphea-like changes in the biopsies (similar to patients 1 and 3) whereas their biopsies show a subacute spongiotic dermatitis with associated vascular ectasia, thrombosis and chronic inflammation (similar to patient 2). Cutaneous scars are complex modalities that require multiple approaches for therapeutic results, from reducing erythema and pruritus to improving function. A staple in the treatment of hypertrophic scars and restrictive scars has been intralesional corticosteroids.[32] Moreover, additional options are now available with recent advances in laser technology. Driven by the desire to help these children, we investigated whether laser treatment in combination with fractional epidermal grafting could restore a more normal appearance. We hypothesized that patients with late radiation changes similar to morphea may benefit from fractional laser treatment, whereas patients with more thrombosis and telangiectasias may benefit from PDL. In addition, both types of radiation dermatitis showed significant abnormality in the epidermis. We hypothesized that replacing this diseased epidermis can lead to normalization of not only the epidermis, but the dermis as well through feedback loops and stem-cell involvement.

Despite the limitation of the case series where patients are being treated in a developing country with limited resources (ie, the equipment used was donated by laser companies to our nonprofit organization dedicated to the free, safe, and effective treatment of children with disfiguring birthmarks in Vietnam),[45] we have shown some promising results for the potential use of laser therapy as well as fractional epidermal micrografting in improving radiation-induced dermatitis and fibrosis. More studies as well as immunohistochemical and histological analyses may help us better understand the skin's response to these interventions and design the most effective strategy to help these young children achieve a normal function and appearance. Potentially, this strategy may be used to help cancer patients with severe fibrosis and scars from radiation treatment and can pave the way to help patients with other debilitating fibrotic diseases in dermatology such as scleroderma, morphea, or nephrogenic systemic fibrosis.

References

1. Lee JW, Zoumalan RA, Valenzuela CD, et al. Regulators and mediators of radiation-induced fibrosis: Gene expression profiles and a rationale for Smad3 inhibition. Otolaryngol Head Neck Surg. 2010;143(4):525-530.
2. Delanian S, Lefaix JL. Current management for late normal tissue injury: radiationinduced fibrosis and necrosis. Semin Radiat Oncol. 2007;17(2):99-107.
3. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol. 2006;54(1):28-46.
4. Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD Jr. Radiation-induced skin carcinomas of the head and neck. Radiat Res. 1991;125(3): 318-325.
5. Davis MM, Hanke CW, Zollinger TW, Montebello JF, Hornback NB, Norins AL. Skin cancer in patients with chronic radiation dermatitis. J Am Acad Dermatol. 1989;20(4):608-616.
6. Shore RE. Radiation-induced skin cancer in humans. Med Pediatr Oncol. 2001;36(5):549-554.
7. Martin M, Lefaix J, Delanian S. TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys. 2000;47(2): 277-290.
8. Sivan, V., et al. Altered proliferation and differentiation of human epidermis in cases of skin fibrosis after radiotherapy. Int J Radiat Oncol Biol Phys. 2002;53(2):385-393.
9. Nymann P, Hedelund L, Haedersdal M. Intense pulsed light vs. long-pulsed dye laser treatment of telangiectasia after radiotherapy for breast cancer: a randomized splitlesion trial of two different treatments. Br J Dermatol. 2009;160(6):1237-1241.
10. Kim DH, Ryu HJ, Choi JE, Ahn HH, Kye YC, Seo SH. A comparison of the scar prevention effect between carbon dioxide fractional laser and pulsed dye laser in surgical scars. Dermatol Surg. 2014:40(9):973-978.
11. Brewin MP, Lister TS. Prevention or treatment of hypertrophic burn scarring: a review of when and how to treat with the pulsed dye laser. Burns. 2014;40(5):797-804.
12. Hultman CS, Friedstat JS, Edkins RE, Cairns BA, Meyer AA. Laser resurfacing and remodeling of hypertrophic burn scars: the results of a large, prospective, before-after cohort study, with long-term follow-up. Ann Surg. 2014;260(3):519-29; discussion 529-532.
13. Manuskiatti W, Wanitphakdeedecha R, Fitzpatrick RE. Effect of pulse width of a 595-nm flashlamp-pumped pulsed dye laser on the treatment response of keloidal and hypertrophic sternotomy scars. Dermatol Surg. 2007;33(2):152-161.
14. Parrett BM, Donelan MB. Pulsed dye laser in burn scars: current concepts and future directions. Burns. 2010;36(4):443-449.
15. Alster TS, Handrick C. Laser treatment of hypertrophic scars, keloids, and striae. Semin Cutan Med Surg. 2000;19(4):287-292.
16. Liew SH, Murison M, Dickson WA. Prophylactic treatment of deep dermal burn scar to prevent hypertrophic scarring using the pulsed dye laser: a preliminary study. Ann Plas Surg. 2002;49(5):472-475.
17. Gladsjo JA, Jiang SI. Treatment of surgical scars using a 595-nm pulsed dye laser using purpuric and nonpurpuric parameters: a comparative study. Dermatol Surg. 2014;40(2):118-126.

18. Kwan JM, Wyatt M, Uebelhoer NS, Pyo J, Shumaker PR. Functional improvement after ablative fractional laser treatment of a scar contracture. PM R. 2011;3(10):986-987.
19. Uebelhoer NS, Ross EV, Shumaker PR. Ablative fractional resurfacing for the treatment of traumatic scars and contractures. Sem Cutan Med Surg. 2012;31(2):110-120.
20. Choi JE, Oh GN, Kim JY, Seo SH, Ahn HH, Kye YC. Ablative fractional laser treatment for hypertrophic scars: comparison between Er:YAG and CO_2 fractional lasers. J Dermatolg Treat. 2014;25(4):299-303.
21. Kineston D, Kwan JM, Uebelhoer NS, Shumaker PR. Use of a fractional ablative 10.6-µm carbon dioxide laser in the treatment of a morphea-related contracture. Arch Dermatol. 2011;147(10):1148-1150.
22. Grunewald S, Bodendorf M, Illes M, Kendler M, Simon JC, Paasch U. In vivo wound healing and dermal matrix remodelling in response to fractional CO(2) laser intervention: clinicopathological correlation in non-facial skin. Int J Hyperthermia. 2011;27(8): 811-818.
23. Helbig D, Bodendorf MO, Grunewald S, Kendler M, Simon JC, Paasch U. Immunohistochemical investigation of wound healing in response to fractional photothermolysis. J Biomed Opt. 2009;14(6):064044.
24. Orringer JS, Kang S, Johnson TM, et al. Connective tissue remodeling induced by carbon dioxide laser resurfacing of photodamaged human skin. Arch Dermatol. 2004;140(11):1326-1332.
25. Capon A, Mordon S. Can thermal lasers promote skin wound healing? Am J Clin Dermatol. 2003;4(1):1-12.
26. Hantash BM, Mahmood MB. Fractional photothermolysis: a novel aesthetic laser surgery modality. Dermatol Surg. 2007;33(5):525-534.
27. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med. 2004;34(5):426-438.
28. Rahman Z, MacFalls H, Jiang K, et al. Fractional deep dermal ablation induces tissue tightening. Lasers Surg Med. 2009:41(2):78-86.
29. Tierney EP, Hanke CW, Watkins L. Treatment of lower eyelid rhytids and laxity with ablative fractionated carbon-dioxide laser resurfacing: case series and review of the literature. J Am Acad Dermatol. 2011;64(4):730-740.
30. Spandau DF, Lewis DA, Somani AK, Travers JB. Fractionated laser resurfacing corrects the inappropriate UVB response in geriatric skin. J Invest Dermatol. 2012;132(6):1591-1596.
31. Makboul M, Makboul R, Abdelhafez AH, Hassan SS, Youssif SM. Evaluation of the effect of fractional CO_2 laser on histopathological picture and TGF-ß1 expression in hypertrophic scar. J Cosmet Dermatol. 2014;13(3):169-179.
32. Waibel JS, Wulkan AJ, Shumaker PR. Treatment of hypertrophic scars using laser and laser assisted corticosteroid delivery. Lasers Surg Med. 2013;45(3):135-140.
33. Hædersdal M, Sakamoto FH, Farinelli WA, Doukas AG, Tam J, Anderson RR. Fractional CO(2) laser-assisted drug delivery. Lasers Surg Med. 2010;42(2):113-122.
34. Hasegawa T, Suga Y, Ikejima A, et al. Suction blister grafting with CO(2) laser resurfacing of the graft recipient site for vitiligo. J Dermatol. 2007;34(7):490-492.

35. Czajkowski R. Comparison of melanocytes transplantation methods for the treatment of vitiligo. Dermatol Surg. 2004;30(11):1400-1405.
36. de Leeuw J, Assen YJ, van der Beek N, Bjerring P, Martino Neumann HA. Treatment of vitiligo with khellin liposomes, ultraviolet light and blister roof transplantation. J Eur Acad Dermatol Venereol. 2011;25(1):74-81.
37. Tang WY, Chan LY, Lo KK. Treatment of vitiligo with autologous epidermal transplantation using the roofs of suction blisters. Hong Kong Med J. 1998;4(2):219-224.
38. Purschke M, Asrani FA, Sabir SA, Farinelli WA, Anderson RR. Novel methods for generating Fractional Epidermal Micro-Grafts [published online ahead of pring October 11, 2014]. Br J Dermatol. doi:10.1111/bjd.13468.
39. Cho SB, Lee SJ, Chung WS, Kang JM, Kim YK. Treatment of burn scar using a carbon dioxide fractional laser. J Drugs Dermatol. 2010;9(2):173-175.
40. Cervelli V, Gentile P, Spallone D, et al. Ultrapulsed fractional CO_2 laser for the treatment of post-traumatic and pathological scars. J Drugs Dermatol. 2010;9(11):1328-1331.
41. Nowak KC, McCormack M, Koch RJ. The effect of superpulsed carbon dioxide laser energy on keloid and normal dermal fibroblast secretion of growth factors: a serum-free study. Plast Reconstr Surg. 2000;105(6):2039-2048.
42. Chan HH, Wong DS, Ho WS, Lam LK, Wei W. The use of pulsed dye laser for the prevention and treatment of hypertrophic scars in chinese persons. Dermatol Surg. 2004;30(7):987-994; discussion 994.
43. Kuo YR, Wu WS, Jeng SF, et al. Suppressed TGF-beta1 expression is correlated with up-regulation of matrix metalloproteinase-13 in keloid regression after flashlamp pulsed-dye laser treatment. Lasers Surg Med. 2005;36(1):38-42.
44. Kuo YR, Jeng SF, Wang FS, et al. Flashlamp pulsed dye laser (PDL) suppression of keloid proliferation through down-regulation of TGF-beta1 expression and extracellular matrix expression. Lasers Surg Med. 2004;34(2):104-108.
45. Vietnam Vascular Anomalies Center. http://www.vietnamvac.org. Accessed 02/24/2015.

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[7]Beckman Laser Institute and Medical Clinic, Irvine, California.

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