
Increased dermal angiogenesis after low-intensity laser therapy for a chronic radiation ulcer determined by a video measuring system

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Acute and chronic radiation-induced dermatitis can occur after high doses of ionizing radiation of the skin. We describe a patient with a long-lasting radiotherapy-induced ulcer that healed after low-intensity laser therapy. A video measuring system was used to determine the number of dermal vessels in the ulcer before and after laser treatment. We found a statistically significant increase in the number of dermal vessels after low-intensity laser therapy in both the central and marginal parts of the ulcer compared with its pretreatment status. (*J Am Acad Dermatol* 1999;40:481-4.)

High doses of ionizing radiation of the skin can be followed by both acute and chronic radiodermatitis.¹ The incidence of radiation-induced necroses and ulcers after x-ray therapy depends on the radiation protocol and dose, as well as on the patient's age at the time of irradiation.² Moreover, there is evidence for an elevated risk of skin malignancies as a late complication after radiation therapy.^{1,2} Treatment of hemangiomas with ionizing radiation was performed several decades ago but has been abandoned in the recent past because of possible acute and chronic radiation damage.^{3,4} The histopathologic findings of chronic radiation dermatitis are characterized by thinning of the epidermis, fibrosis of the dermis, obliteration of small arteries, and reduction of capillaries in number and size. Moreover, partial or complete loss of skin appendages is noted.^{1,5} Because of the poor healing tendency of radiation ulcers, surgical intervention may be necessary in some cases to close the

defects. Recently, low-intensity laser irradiation using athermic radiation with wavelengths in the red and infrared region has gained increasing interest as a noninvasive method for the induction of wound healing in such cases.^{6,7} We describe a patient with a long-lasting radiotherapy-induced ulcer that healed after low-intensity laser therapy. A video measuring system (VMS)⁸ was used to determine the number of dermal vessels in the ulcer before and after laser treatment.

CASE REPORT

A 28-year-old female patient presented with an ulcer on the left cervical region, which had been present for 6 months. She had received a series of topical radium treatments for a hemangioma at this site 25 years earlier. The partially necrotic ulcer, measuring 18 mm², was surrounded by telangiectases. A 2-mm punch biopsy was taken that confirmed the diagnosis of an ulcerous radiodermatitis. In view of previously reported results with low-intensity laser irradiation for the induction of wound healing in recalcitrant radiation ulcers^{6,7} and because other conventional treatments had failed to induce healing, we initiated low-intensity laser therapy.

MATERIAL AND METHODS

Laser therapy was carried out in an outpatient setting with a helium/neon (He:Ne) laser device (wavelength, 632.8 nm; power output, 10 mW; energy density at skin level, 30 J/cm²) twice weekly.

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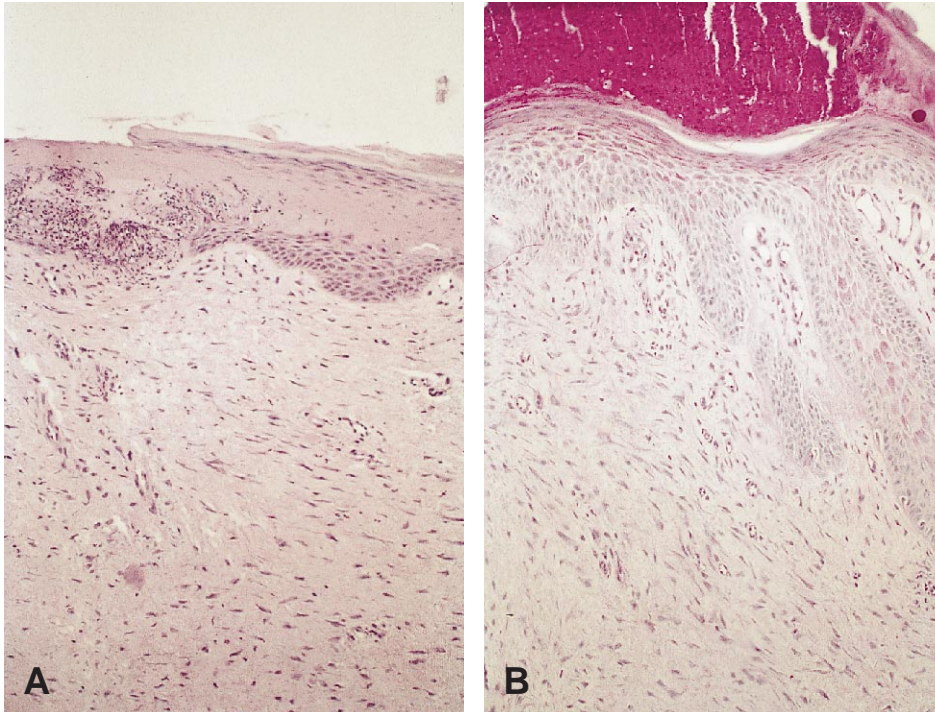


Fig 1. Histologic characteristics of radiation ulcer before (**A**) and after (**B**) low-intensity laser treatment. (**A**, Hematoxylin-eosin stain; **B**, periodic acid-Schiff stain; original magnifications: **A** and **B**, $\times 80$.)

Skin biopsy specimens were obtained from lesional (center and margin) and adjacent (surrounding) skin of the ulcer before the initiation of laser therapy and after complete wound closure as well as from the contralateral side of the neck. Biopsy specimens were processed for hematoxylin-eosin and periodic acid-Schiff (PAS) staining. To determine the number of intradermal vessels in PAS-stained sections we used a video measuring system. Video prints (Mitsubishi V1A 100 video printer, Mitsubishi, Japan) were obtained from each of the 5 consecutive histologic sections.

By drawing one horizontal analyzing line marking the dermoepidermal junction and two parallel vertical analyzing lines in a distance of $500\ \mu\text{m}$ (B , P_1) at scanning magnification, 3 areas of equal size ($500 \times 750\ \mu\text{m}$) were defined: the margin of the ulcer (MU: area between the two vertical analyzing lines B and P_1 , the center of the ulcer (CU: corresponding area adjacent left of the MU area), and the surrounding skin (SS: corresponding area adjacent right to the MU area). The number of dermal vessels of 5 subsequent sections of the MU, CU, and SS area was averaged and mean numbers of vessels before and after laser treatment were then compared using Student's *t* test. Values of *P* less than .05 were regarded as statistically significant.

RESULTS

After 4 weeks and a total of 7 irradiations, the ulcer had healed completely. Histologic examination of the affected skin before treatment showed an atrophic epidermis and flattened rete ridges. The ulcer was covered by necrotic cells, fibrin, and neutrophil granulocytes (Fig 1, *A*). Fibroblasts in the dermis below the ulcer had bizarre shapes and were reduced in number compared with normal skin. Light microscopy in combination with a VMS revealed a decreased number of vessels in both the center and the margin of the ulcer before laser treatment compared with normal skin (Fig 2, *A*). The number of capillaries in the ulcer's surrounding skin, however, did not differ from normal skin. After wound closure, an increased number of vessels was noted compared with both pretreatment conditions and normal skin (Figs 1, *B*, and 2, *B*).

Statistical analysis revealed a significant increase in the number of dermal vessels after low-intensity laser therapy in both the central (125%) and the marginal (263%) parts of the ulcer, as compared with the pretreatment status (Table I).

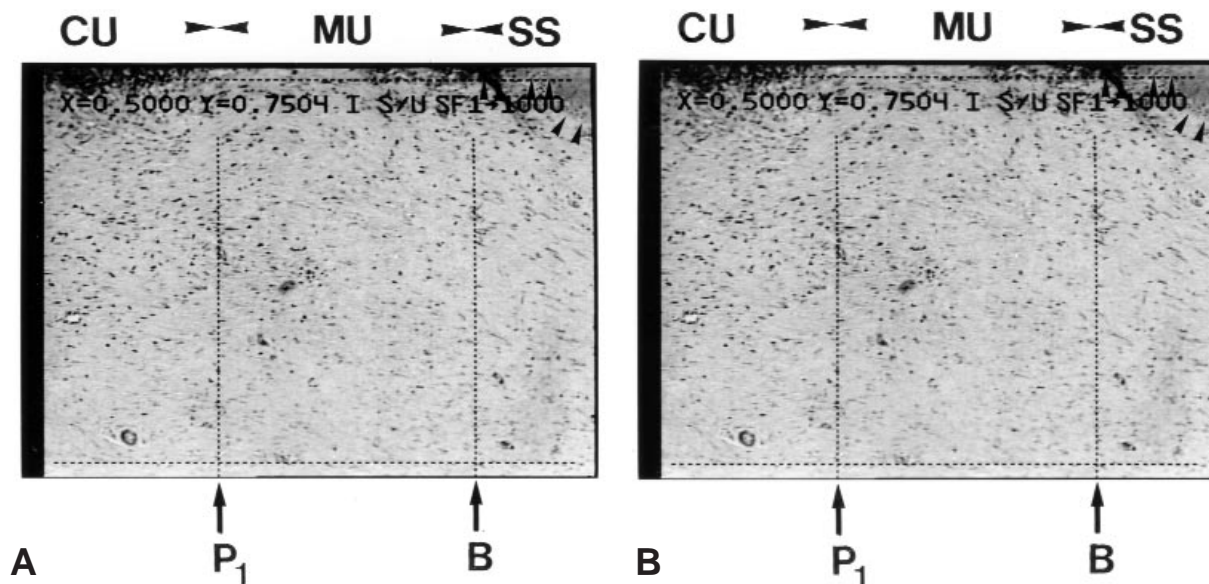


Fig 2. Print of the VMS ($\times 120$) displays histologic features of radiation ulcer before (A) and after (B) low-intensity laser treatment. By drawing one horizontal analyzing line marking the dermoepidermal junction (arrows) and two parallel vertical analyzing lines in a distance of $500 \mu\text{m}$ (B, P_1) at scanning magnification, three areas of equal size ($500 \times 750 \mu\text{m}$) were defined (CU, center of ulcer; MU, margin of ulcer; SS, surrounding skin adjacent to the ulcer) for quantification of vessel numbers.

Table I. Quantification of dermal vessel number by a video measuring system

	Normal skin			Ulcer before laser treatment			Ulcer after laser treatment		
	C	M	B	CU	MU	SS	CU	MU	SS
No. of vessels (mean \pm SD)	10.8 ± 2.5	10.6 ± 1.9	7.4 ± 1.9	6.2 ± 0.8	4.4 ± 0.9	9.0 ± 1.3	14.0 ± 2.3	18.0 ± 1.0	8.2 ± 1.5
Statistical analysis before/after treatment							$P < .001$	$P < .001$	NS

Statistical comparison of vessel numbers in comparable $500 \times 750 \mu\text{m}$ areas in upper dermal tissue before versus after low-intensity laser treatment. Five consecutive sections of each biopsy specimen were evaluated. Analysis was performed by Student's *t* test. B, Border of specimen from normal skin; C, center of specimen from normal skin; CU, center of ulcer; M, margin of specimen from normal skin; MU, margin of ulcer; SS, surrounding skin adjacent to ulcer.

DISCUSSION

This article demonstrates the complete healing of a chronic radiation ulcer after low-intensity laser irradiation. By means of light microscopy in combination with a VMS we found a significant increase in the number of dermal vessels after laser therapy in the re-epithelialized skin compared with pretreatment conditions. To our knowledge, this is the first report on the quantitative determination of the intradermal number of vessels after low-intensity laser irradiation. Previous studies evaluating the histologic changes after laser therapy in the

process of wound healing mainly concerned collagen synthesis and tensile strength.⁹⁻¹¹

The VMS represents a useful tool to quantify the number of intradermal structures and has been used successfully in the quantification of elastic fibers.⁸ Because pathogenetic changes in radiation ulcers are confined to the upper and mid-dermal tissue, this method appears to be appropriate for this particular investigation.

The results obtained in the present study are in accordance with previous data of our group^{6,7,12} and others.¹³ Recently Yu, Naim, and Lanzafame¹⁴

applied a score system for the evaluation of biopsy specimens based on the degree of re-epithelialization, granulation tissue formation, collagen deposition, and vascularity for the assessment of wound healing in diabetic mice. Their results showed improvement in all these parameters in the laser-treated wounds compared with sham-irradiated controls.

Regarding the mechanism of action, there is evidence that low-intensity laser irradiation is able to induce neovascularization *in vitro*¹⁵ and *in vivo*,¹⁶ to improve skin circulation in conditions of microangiopathy,¹⁷ and to minimize tissue damage caused by ischemia.¹⁸ In addition, it has been demonstrated that this type of athermic phototherapy can stimulate certain cellular functions such as protein synthesis and mitotic rate,¹⁹ increase keratinocyte growth rate and motility,^{20,21} and induce the release of growth factors involved in wound healing²² such as cytokines and basic fibroblast growth factor.²³⁻²⁵

In conclusion, we demonstrate another case of successful treatment of a chronic radiation ulcer by low-intensity laser therapy histologically characterized by a significant increase in intradermal vessel numbers determined by a VMS. Because low-intensity laser irradiation represents a noninvasive treatment, it may be considered as an alternative to complex surgical interventions of recalcitrant radiation ulcers.

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