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COMMENTARY

Photobiomodulation therapy: management of mucosal necrosis of the oropharynx in previously treated head and neck cancer patients

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Abstract Necrosis of the oral mucosa following head and neck cancer radiation therapy presents considerable clinical management challenges. We report three cases of symptomatic persisting oral ulcerations where the addition of photobiomodulation therapy resulted in a rapid resolution of the oral lesions and in patient symptoms. These cases suggest that photobiomodulation may represent an adjunct to care of these difficult to manage complications in oncology.

Keywords Photobiomoduation · Low level laser therapy · Mucosal wound healing · Post-radiation mucosal necrosis

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Post radiation fibrosis and risk of oral mucosal ulceration and osteonecrosis are known risks of a high-dose radiation therapy, even with intensity modulated radiation therapy (IMRT) and proton beam techniques. Management of these lesions requires a confirmation of the absence of malignancy, promotion of conservative wound healing, and prevention of further injury; however, an effective management is challenging, and patients may suffer from persisting and symptomatic lesions and limited oral function.

Photobiomodulation (PBM) therapy, previously known as the low-level laser therapy (LLLT), has been shown to promote a repair of bone and connective tissue, by biostimulation of cellular repair, angiogenesis, and anti-inflammatory effects [1–6]. These features suggest a potential role for PBM in modulation/repair of chronic wounds that may be applicable in the management of oral soft tissue necrosis following head and neck radiation therapy (RT).

We treated three patients with chronic postradiation oral mucosal wounds with the addition of PBM therapy to clinical care. PBM therapy was provided twice weekly to the sites of necrosis following the methods as recently described [7].

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Case 1: a 45-year-old male treated for adenoid cystic carcinoma (ACC) of the hard palate, T4aN0M0 (Stage IVa) with surgical resection, and postoperative RT (6000 cGy) (IMRT) developed a soft palate ulceration and discomfort on swallowing 15 months following RT. Biopsy provided a diagnosis of chronic mucosal ulceration without ACC. The ulcer had defined borders without clinical erythema and measured 15 × 12 mm (Fig. 1). Rapid resolution was seen in 4 weeks of PBM treatment and symptoms improved. At 6 weeks, the ulceration was resolved, the borders of the ulcer were remodeled, and the normal tissue contours were seen (Fig. 2). Resolution was confirmed on oral exam and fiberoptic scope examination.

Case 2: a 55-year-old male was referred with a necrotic ulcer of the right tonsil fossa. He had a 30-year history of HIV when seen with undetectable viral load, absolute CD4 165, and CD4/CD8 0.25.

The first tonsil cancer in the right tonsil (T4aN2aM0) was treated with cisplatin and five fluorouracil and concurrent RT (6000 cGy). The second cancer of the left tonsil (T1N0M0, HPV+, SCC) was treated 5 years later with cetuximab and RT (5040 cGy) (IMRT) and boost dose to the right tonsil primary (6600 cGy). Four months following RT, he developed a necrotic ulcer in the right tonsil fossa. He had severe trismus, (interincisal opening 18 mm), xerostomia, and an area of osteonecrosis of the right mandible following an infection around the lower left third molar that was extracted 5 months earlier. He had

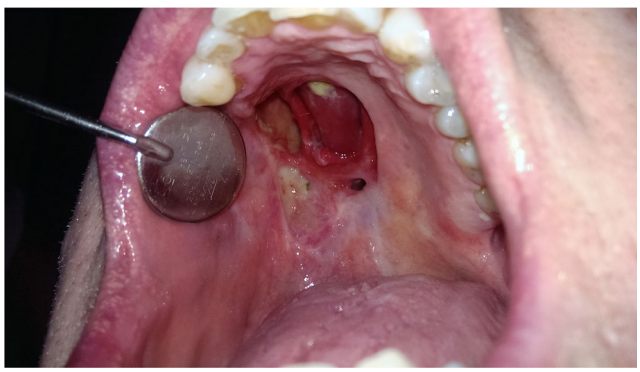

Fig. 1 Mucosal necrosis pretreatment

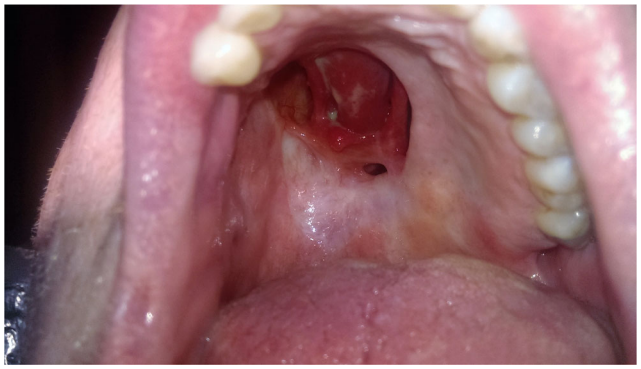

Fig. 2 Resolution of ulceration

esophageal stricture and was PEG-tube dependent. Due to the persisting tonsil ulceration (measuring 5 × 8 mm), he was treated with PBM beginning 8 months following the treatment of the second tonsil cancer and to the area of osteonecrosis of the left mandible. Aqueous chlorhexidine rinse (0.12%) was provided for irrigation of the site of osteonecrosis and for oral rinsing due to a limited access for oral hygiene. He was also prescribed pentoxifylline and vitamin E due to tissue necrosis and also began physiotherapy for trismus. The ulcer in the right tonsil fossa was resolved in 3 weeks of PBM therapy. There were no changes in interincisal opening. The area of bone necrosis appeared clinically covered by mucosa after 4 weeks of PBM.

Case 3: a 58-year-old male who was seen after he developed an ulcerative perforation of the left soft palate. He had a remote history of non-Hodgkin lymphoma as a teenager, treated with a total lymphoid irradiation (5000 cGy). Due to diagnosis of T2N0M0, HPV+ SCC of the left tonsil, he received IMRT (tumor dose: 6550 cGy). When seen, he was feeding-tube dependent due to esophageal stricture. Pain management included fentanyl (37.5 μg), morphine suspension (4 mg by PEG-tube, revised to J-tube), and oxycodone 15 mg for breakthrough pain.

He developed a full thickness ulceration of the left soft palate (10 × 5 mm) 6 months following RT for tonsil SCC, without evidence of SCC at that site. Pain resolved within 2 weeks of PBM therapy, analgesics were discontinued, and the lesion rapidly improved and was clinically resolved after 4 weeks of treatment.

Mucosal lesions following photobiomodulation therapy

Pt #	Onset of oral ulcer	Biopsy	Pretreatment		Posttreatment		
			Mucosal pain[a]	Mucosal erythema[b]	Pre PBM mucosal ulceration	Resolution post PBM (weeks of treatment)	Pain[a] Erythema[b] Ulceration
1	14 mos post RT	Chronic ulcer NOS, immovable soft palate	3	0	15 × 12 mm	6 weeks	0
2	6 mos post 2nd RT	–	5	2	R tonsil 5 × 8 mm	3 weeks	0
3	Post radiation therapy	–	4	2	10 × 5mm	4 weeks	0

Mucosal pain[a] visual analog scale (0–10, with 10 representing "pain as bad as it could be")

Mucosal erythema[b] 0-none, 1-mild, 2-moderate, 3-severe

mos months, *RT* radiation therapy, *NOS* nonspecific

Discussion

Prior studies support a potential benefit of PBM in the healing of bone and soft tissue. Infrared laser has been used to stimulate the repair of osteonecrosis (five LLLT sessions in 2 weeks, 0.053 J/cm^2 × 15 min) in two patients with resolution, and five others with partial healing of the lesion [8–11] with good results in bone healing [12].

In the cases presented in this report, rapid resolution of chronic mucosal lesions due to RT was seen with the addition of PBM treatments. The PBM treatments were well-tolerated, and the rapid response supports suggestions that PBM promoted wound healing of soft tissue necrosis. The cases described a suggestion that a minimum of twice weekly treatment should be considered for 4 weeks to assess a potential response to PBM therapy. Controlled trials appear indicated based upon the findings in these cases.

Our current report of mucosal necrosis following RT is consistent with the previous data suggesting the effect of PBM therapy in wound healing. The basic biological mechanism behind the effects of PBM therapy is thought to be absorption of light energy (red and near-infrared photons) by chromophores of the respiratory chain located in mitochondria, leading to an increased enzyme activity and ATP production [13]. For visible and near-infrared wavelengths, chromophores are typically molecules that contain metallic atoms in their structure [14]. Specifically for wound healing, PBM results in cell migration, proliferation, and angiogenesis [15, 16]. These processes can be regulated by growth factors and related to nitric oxide (NO) signaling, which release and production can be modulated by PBM therapy [17–19]. NO may cause a suppression of inflammatory response, vasodilatation, angiogenesis, inhibiting apoptosis, and cell migration. PBM therapy is thought to promote cell proliferation through the activation of the mitochondrial respiratory chain and the initiation of cellular signaling [20]. PBM therapy caused a 3.1-fold significant increase in newly formed blood vessels 6 days post infarction, as compared with non-irradiated rats. Neovascularization may also be mediated by matrix metaloproteases (MMP) [21]. PBM therapy can up-regulate the production of MMP-2 (gelatinase) and transforming growth factor (TGF)-β1 in cultured human keratinocytes, endothelial cells and fibroblasts [22].

Studies have also shown that PBM therapy enhances the tensile strength of cutaneous wound in a murine diabetic model promoting an earlier consolidation of scar tissue. Wounds illuminated with (830 nm, 20 J/cm^2) or (685 nm, 20 J/cm^2) showed a better quality of granulation tissue formation (more production and organization of collagen) than the ones illuminated with a higher irradiation fluences, suggesting that there is a biphasic dose response [18], and that the enhancement of granulation is possible with PBM therapy [23].

This clinical report shows the potential utility of PBM therapy in the healing of mucosal injury/necrosis induced by cancer radiotherapy for head and neck cancer. These cases suggest a potential therapeutic option for cancer patients with necrosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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