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BRIEF REPORTS

Hyperbaric oxygen therapy: An alternative treatment for radiation-induced cutaneous ulcers

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ABSTRACT

Radiotherapy is a widely recognised treatment for non-melanoma skin cancer. We report three cases of radiation-induced skin ulcers in which hyperbaric oxygen therapy was administered in 90-min sessions, 5 days a week at 2.4 absolute atmospheres in a multiplace hyperbaric chamber. Hyperbaric oxygen therapy is an outpatient treatment that does not displace other classical treatments and may be used as an adjunct therapy.

Key words: soft-tissue radionecrosis, hyperbaric oxygen.

WHAT THIS RESEARCH ADDS

- Exposing soft tissue to high-dose radiation often causes acute or delayed skin ulcers that can become intractable as a result of improper wound healing.
- Hyperbaric oxygen therapy does not displace other, classical treatments, but may be used as an adjunct therapy.

INTRODUCTION

Radiation therapy is one of the main treatments employed for the management of non-melanoma skin cancer. However, the exposure of soft tissue to high-dose radiation often causes acute or delayed skin ulcers that can become intractable as a result of improper wound healing, infection or both. Hyperbaric oxygen therapy is a therapeutic option for this condition that increases the oxygen supply to tissues by enhancing angiogenesis and collagen synthesis, and thus promotes wound healing. We present three patients with radio-induced skin ulcers that were successfully treated using hyperbaric oxygen therapy.

CASE REPORT 1

A 73-year-old man with a history of hypertension, ischaemic heart disease and morbid obesity was diagnosed with a squamous cell carcinoma in his left leg. He was treated with radical hypofractionated radiation therapy (55 Gy). One year later he developed many skin ulcers, which did not respond to topical treatment. Several skin biopsies were obtained and the presence of cancer was ruled out. Hyperbaric oxygen therapy treatment was then administered in 90-min sessions, 5 days a week at 2.4 ATA (atmosphere absolute) in a multiplace hyperbaric chamber. Complete healing was observed after 55 sessions (Fig. 1). The patient remains asymptomatic after 18 months.

CASE REPORT 2

A 50-year-old woman with no other relevant medical conditions was diagnosed with a squamous cell carcinoma located in the anal canal presenting vulvovaginal extension (T4N2M0, stage IIIB), which was treated using radical radiotherapy (54 Gy) and concomitant chemotherapy (mitomycin and 5-fluorouracil). Three months after the radiotherapy the patient developed a proctitis and a painful perianal skin ulcer. A skin biopsy ruled out cancer. Hyperbaric oxygen therapy was then initiated in a multiplace hyperbaric chamber in 90-min sessions, 5 days a week at 2.4 ATA. The ulcer was completely healed after 37 sessions

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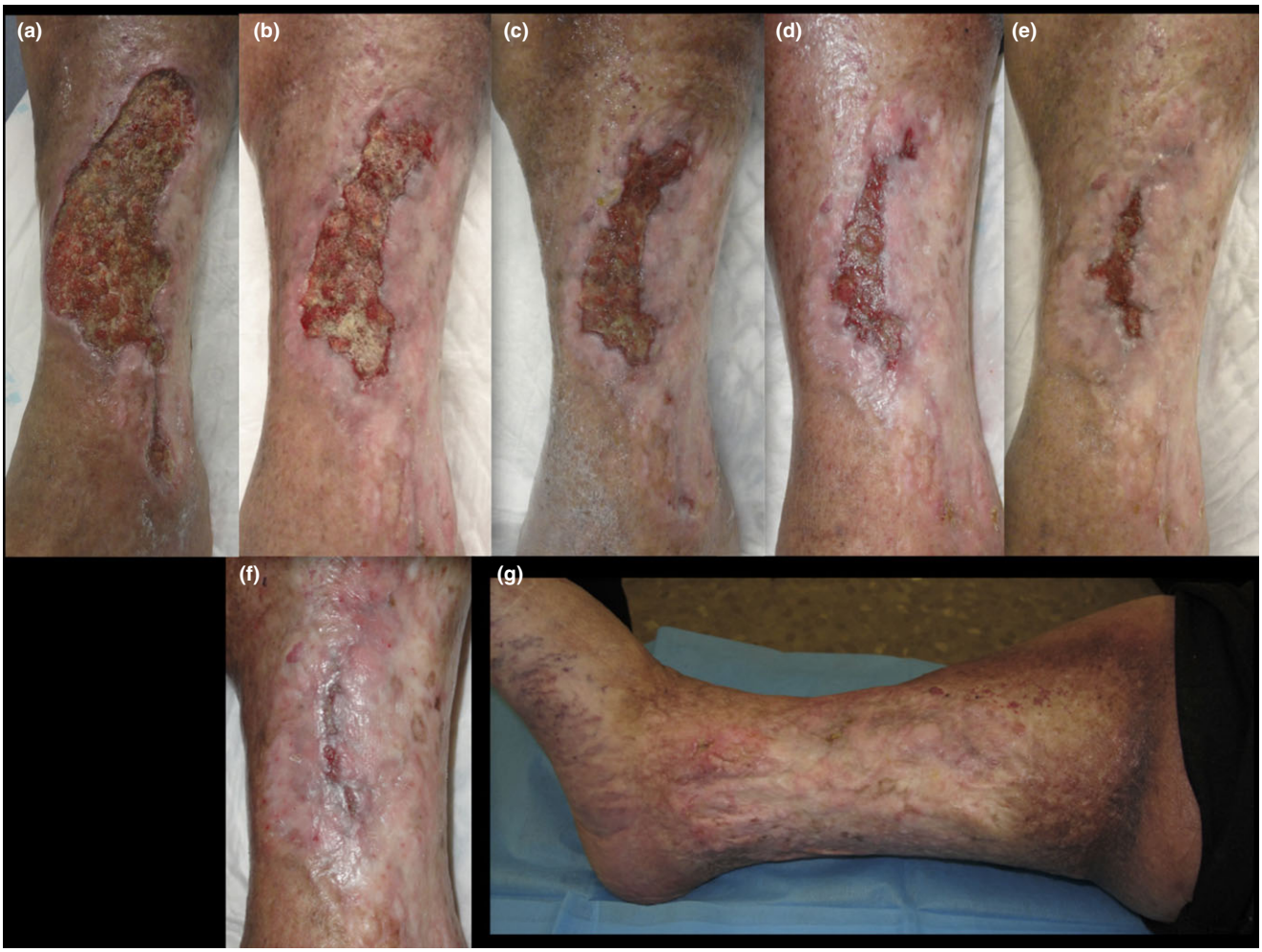

Figure 1 (a–f) Evolution of ulcers during treatment with hyperbaric oxygen therapy. (g) Appearance of the limb 18 months after the conclusion of hyperbaric oxygen therapy.

(Fig. 2). The patient has had no ulcer recurrence after 12 months.

CASE REPORT 3

A 55-year-old man with no relevant medical history underwent the surgical removal of a squamous cell carcinoma in the right heel. As the deep surgical margin was affected, adjuvant brachytherapy (42 Gy) was then administered. Five months after this radiotherapy an intensely painful skin ulcer appeared (Fig. 3). A skin biopsy ruled out cancer. The patient was then given 90-min sessions of hyperbaric oxygen therapy, 5 days a week at 2.4 ATA in a multiplace hyperbaric chamber. After 28 sessions a complete response was obtained and after 6 months the patient remains asymptomatic, with no signs of recurrence.

DISCUSSION

Soft-tissue radionecrosis is one of the various complications of radiotherapy. Its incidence is falling with the growing use of high-energy equipment, but if it does occur there are no standard therapeutic guidelines for addressing the condition. Surgery is not considered the gold standard, given the high rate of postoperative complications. Radionecrosis is caused by progressive obliterating endarteritis that results in a vascular stenosis and a fibroatrophic effect that leads to stromal fibrosis.[1] In this fibrous and hypoxic tissue, hyperbaric oxygen therapy acts by increasing the oxygen supply, stimulating angiogenesis, reducing fibrosis and mobilising and increasing stem cells, thus accelerating the healing process.[2–5] There have been several studies of hyperbaric oxygen therapy for radiation-induced skin ulcers but most of these are only brief case series. The largest such study included 58 patients and reported an excellent response, with resolution in 25% of the patients and an improvement of 50–90% in half of the patients.[6] Cases have also been reported of a successful response in skin ulcers in the lower limbs,[7] the breast[8] or the anorectal area.[9]

Hyperbaric oxygen therapy is a physical therapy that achieves high partial pressures of oxygen by providing

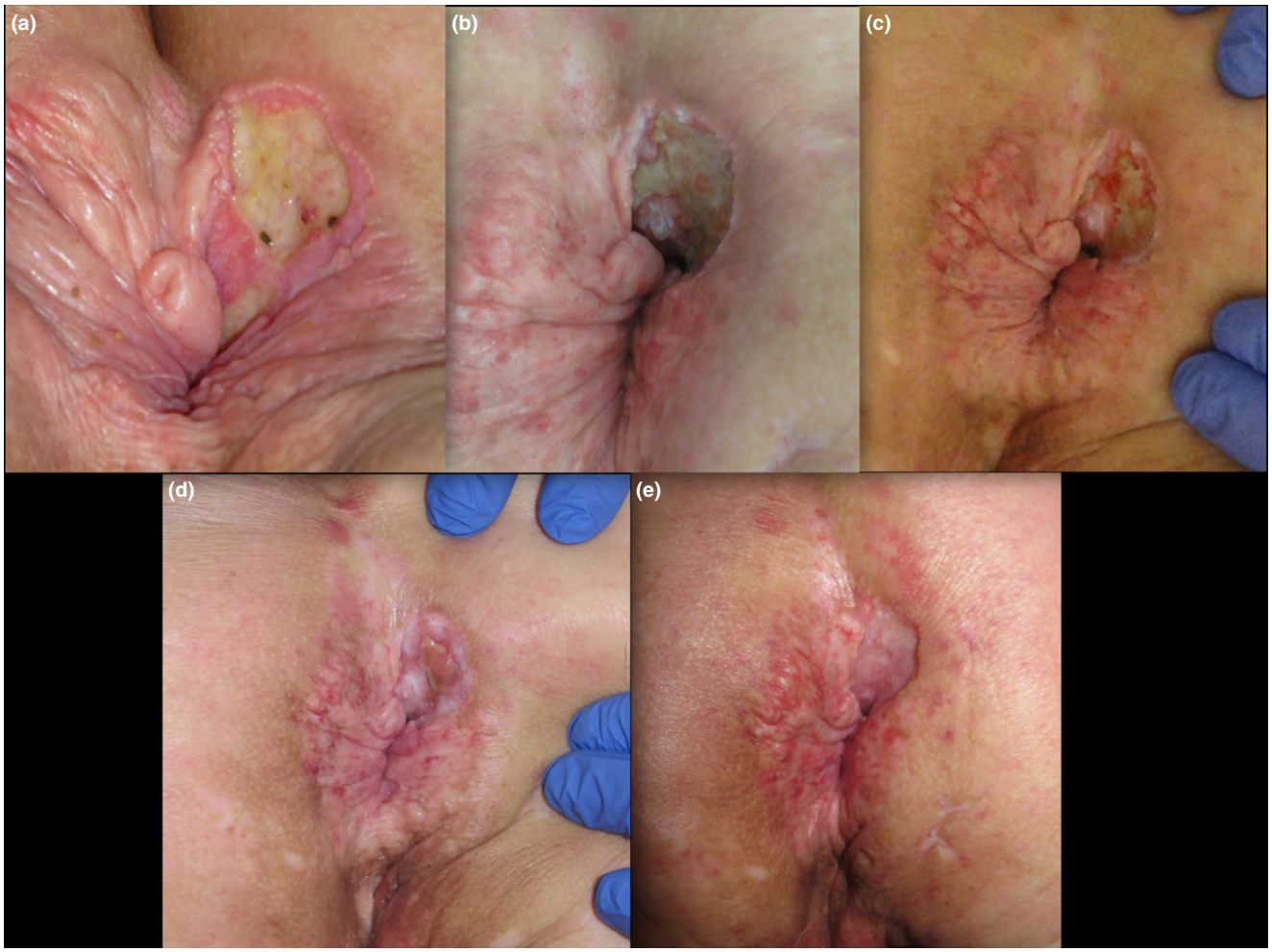

Figure 2 (a) The ulcer at 3 months after the conclusion of radiotherapy of the anal canal. (b–e) Evolution of the ulcer during treatment with hyperbaric oxygen therapy, until final healing.

pure oxygen within a chamber at a pressure above atmospheric levels.[10] The administration of 100% oxygen at an ambient pressure of greater than 1.3 ATA is achieved in a closed vessel called a hyperbaric chamber, which may be monoplace or multiplace. Monoplace chambers are essentially acrylic glass tubes pressurised to 3 ATA with pure oxygen and allow only one patient to be treated at a time. Multiplace hyperbaric chambers allow the simultaneous treatment of several patients, at pressures of up to 6 ATA.[11]

The benefits of hyperbaric oxygen therapy are obtained from both a volumetric effect and a solubility effect.[10] The volumetric effect (Boyle's law) is based on the fact that at a constant temperature, the volume of gas is inversely proportional to the pressure. Thus, at a higher ambient pressure there is a decreased volume of the organic cavities that are not in contact with the airway. Based on this effect, the gaseous embolism is one of the main indications for this therapy. The solubility effect (Henry's law) is caused by an increase in the partial pressure of oxygen. By breathing pure oxygen in a hyperbaric environment, a progressive increase in blood pressure, venous and tissue oxygen is obtained. The therapeutic benefits of hyperbaric oxygen therapy, such as the correction of general or local tissue hypoxia, the stimulation of scarring and angiogenesis, the increased phagocytosis of neutrophils, bactericidal and bacteriostatic action, the blockade of clostridial toxin formation and the elimination of carboxyhaemoglobin are produced because of this solumetric effect.[11]

The indications for hyperbaric oxygen therapy have been approved by the Undersea and Hyperbaric Medical Society,[12,13] which has established three types of indications: preferential, complementary and experimental. In the case of radiation-induced lesions, hyperbaric oxygen therapy has a complementary indication as it is not considered an essential treatment, but it does seem to have a beneficial action in the short term.[14]

The main complications of hyperbaric oxygen therapy are related to the changes in pressure and to the toxic effects of oxygen. They are uncommon and they usually appear after long exposures or when higher pressures

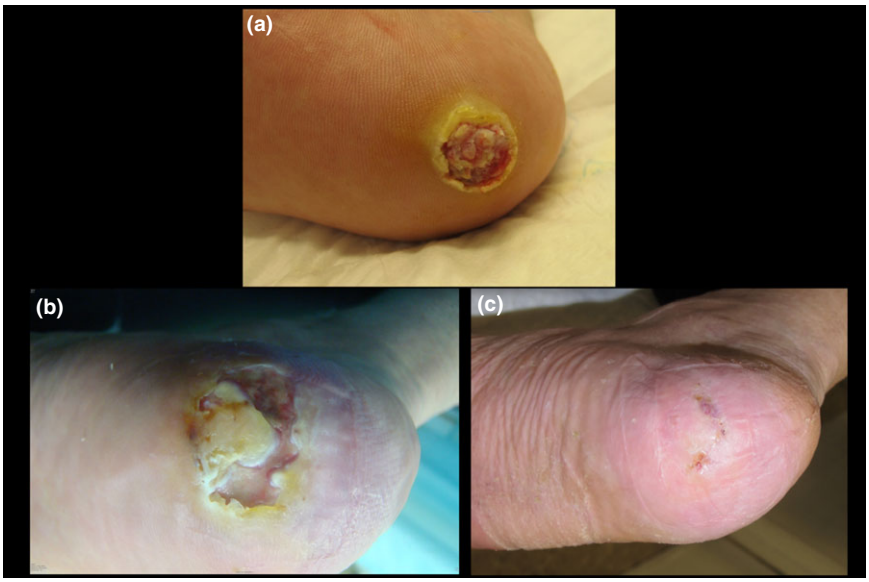

Figure 3 (a) Squamous cell carcinoma of the heel. (b) Ulcer at 5 months after the conclusion of radiotherapy. (c) The ulcer, healed after 28 sessions of hyperbaric oxygen therapy.

than usual are applied. These complications include barotraumatic lesions (which are usually mild and transient), seizures (occurring in one in 2000 patients exposed), retrolental fibroplasia (premature infants) and acute pulmonary oedema (mainly in patients with heart failure or with low ejection fraction or with pulmonary disease or chronic obstructive pulmonary disease).[15]

There are few absolute contraindications to hyperbaric oxygen therapy, the most important of these being untreated pneumothorax, or treatment with doxorubicin (cardiac toxicity) or mafenide acetate (central vasoconstriction).[16]

Concern has been expressed that a therapeutic modality recommended as an adjunct to wound healing and administered to promote the proliferation of fibroblasts, epithelial cells and blood vessels could also lead to a proliferation of malignancies and angiogenesis. In this respect, two literature reviews have been conducted[17,18] analysing 10 studies in humans in which hyperbaric oxygen therapy was used as a radiosensitiser. The results observed were clearly neutral or advantageous in terms of patient survival or incidence of metastases. According to another study that included a large series of patients with head and neck cancer treated with radiotherapy, for whom hyperbaric oxygen therapy was used to treat the adverse effects of radiation therapy, the recurrence rate was higher in the control group (28%) than in the hyperbaric oxygen therapy group (20%).[17]

In conclusion, our patients obtained an excellent clinical response without any adverse effects. It is important to emphasise that the hyperbaric oxygen therapy is an outpatient treatment that does not displace other classical treatments and may be used as an adjunct therapy. Nevertheless, randomised trials should be performed to assess the long-term efficacy of this therapy.

REFERENCES

1. Feldmeier JJ. Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update. *Undersea Hyperb. Med.* 2012; **39**: 1121–39.
2. Thom SR. Hyperbaric oxygen its mechanism and efficacy. *Plast. Reconstr. Surg.* 2011; **127**: 131S–41S.
3. Thom SR, Bhopale VM, Velazquez OC *et al.* Stem cell mobilization by hyperbaric oxygen. *Am. J. Physiol. Heart Circ. Physiol.* 2006; **290**: 1378–86.
4. Goldstein LJ, Gallagher KA, Bauer SM *et al.* Endothelial progenitor cell release into circulation is triggered by hyperoxia induced increases in bone marrow nitric oxide. *Stem Cells* 2006; **24**: 2309–18.
5. Liu ZJ, Velazquez OC. Hyperoxia, endothelial progenitor cell mobilization and diabetic wound healing. *Antioxid. Redox Signal.* 2008; **10**: 1869–82.
6. Hampson NB, Holm JR, Wreford-Brown CE *et al.* Prospective assessment of outcomes in 141 patients treated with hyperbaric oxygen for chronic radiation tissue injury. *Cancer* 2012; **118**: 3860–8.
7. Feldmeier JJ, Heimbach RD, Davolt DA *et al.* Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities. *Undersea Hyperb. Med.* 2000; **27**: 15–9.
8. Enomoto M, Yagishita K, Okuma K *et al.* Hyperbaric oxygen therapy for a refractory skin ulcer after radical mastectomy and radiation therapy: a case report. *J. Med. Case Rep.* 2017; **11**: 5.
9. Bem J, Bem S, Singh A. Use of hyperbaric oxygen chamber in the management of radiation-related complications of the anorectal region: report of two cases and review of the literature. *Dis. Colon Rectum* 2000; **43**: 1435–8.
10. Desola J, Crespo A, García A *et al.* Indicaciones y contraindicaciones de la oxigenoterapia hiperbárica. *JANO/Medicina* 1998; **54**: 5–11.
11. Iriarte JI, Batle JM, Urdain M *et al.* Empleo de la oxigenoterapia hiperbárica en cirugía oral y maxilofacial. *Rev. Esp. Cir. Oral y Maxilofac.* 2006; **28**: 7–24.
12. Feldmeier JJ. Delayed radiation injuries (soft tissue and bony necrosis). In: Weaver LK (ed.). Hyperbaric Oxygen Therapy

Indications, 13th edn. North Palm Beach: Best Publishing, 2014; 13–21.
13. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb. Med.* 2017; **47**: 24–32.
14. Bennett MH, Feldmeier J, Hampson NB *et al.* Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst. Rev.* 2016; **4**: CD005005.
15. Heyboer M, Sharma D, Santiago W *et al.* Hyperbaric oxygen therapy: side effects defined and quantified. *Adv. Wound Care (New Rochelle)* 2017; **6**: 210–24.
16. Kindwall EP, Whelan HT (eds). Hyperbaric Medicine Practice, 3rd edn. North Palm Beach: Best Publishing, 2008.
17. Feldmeier J, Carl U, Hartmann K *et al.* Hyperbaric oxygen: does it promote growth or recurrence of malignancy? *Undersea Hyperb. Med.* 2003; **30**: 1–18.
18. Moen I, Stuhr LEB. Hyperbaric oxygen therapy and cancer, a review. *Target. Oncol.* 2012; **7**: 233–42.