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Case report

Hyperbaric oxygen therapy for radiation-induced brachial plexopathy, a case report and literature review

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ABSTRACT

Aim: To report a case of radiation-induced brachial plexopathy (RIBP) with significant radiographic and clinical improvement after a course of hyperbaric oxygen (HBO).

Background: RIBP is a rare complication after radiotherapy to the neck and axilla. There are no standard treatment options, with empirical use pharmacotherapy being predominately used, which has had mixed results.

HBO is efficacious for the treatment of other severe radiation-induced side effects, however, its benefit in RIBP has conflicting reports.

Case Presentation: A 45-year-old male, with a 33 pack-year smoking history, presented with a 6-month history of a progressive left neck mass. The final diagnosis was unknown primary squamous cell carcinoma of the head and neck. He received intensity-modulated radiation therapy (IMRT) with 70 Gy prescribed to the gross tumor volume (PTV HR) and 56 Gy to the oropharynx, nasopharynx, and bilateral lymphatics (PTV SR) in 35 daily fractions with three cycles of concurrent cisplatin at 100 mg/m^2.

Fifteen months following therapy completion, the patient began to endorse symptoms of left brachial plexopathy. Decadron was prescribed for 2 weeks, trental and vitamin E for 6 months, and HBO. The patient returned for follow-up 2 months after completing 30 dives of HBO at 2.4 atmospheres for 2 hours per session. He reported pain resolution and full range of motion of his left arm.

Conclusions: The best management strategy of RIBP is prevention by reducing total RT doses and close follow-up. However, when RIBP occurs, we recommend treatment with HBO therapy, steroids, trental, and vitamin E as tolerable.

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1. Introduction

Radiation-induced brachial plexopathy (RIBP) is a potential complication for patients receiving radiotherapy (>60–66 Gy) for cancer in the neck or axilla. This irreversible complication can result in complete limb paralysis in 0.2–5 years after the first clinical signs.[1] RIBP typically takes 1–4 years after radiotherapy to develop[2]; however, development has been reported within 2–5 months.[3] Latency time can be affected by fraction size, with smaller fractions demonstrating a longer period before symptom development.[4]

RIBP is diagnosed based on clinical and radiographic evidence and commonly presents with subjective paresthesia or dysaesthesia which usually decreases with developing hypoaesthesia then anaesthesia.[5] If pain develops, it typically evolves later.[6] When present, motor weakness is classically progressive, presents later, and is associated with fasciculations and amyotrophy. CT evidence of RIBP is characterized by distortion of tissue planes and increased density of axillary fat.[7] The typical findings on MRI is hyper-intense signal intensity on T2-weighted images.[8,9] The major electromyography finding is reduced compound muscle action potential across the brachial plexus, reflecting demyelination.[5]

Empirical therapy consists of steroids, gabapentin, opioids, and other analgesics which focuses on improving symptoms but not pathogenesis.[10] Another therapeutic option may be hyperbaric oxygen (HBO) therapy which has proven beneficial when treating other radiation sequelae. HBO is thought to result in a steeper oxygen gradient, stimulating angiogenesis, fibroplasia, and other tissue restorative processes.[11]

We report a case of RIBP occurring 15 months after external beam radiation therapy for head and neck squamous cell carcinoma of unknown primary arising in the left level II cervical lymph nodes. The patient had a complete clinical and radiographic response to HBO therapy.

2. Case background

A 45-year-old male, with a 33 pack-year smoking history, presented with a 6-month history of a progressive left neck mass associated with left-sided neck pain, otalgia, left-sided odynophagia, and episodes of dysphagia. The patient denied brachial plexopathy symptoms. Neck CT with contrast and PET/CT showed a 3.2 × 2.8 cm complex cystic mass within the cervical level II region of the left neck with compression of the jugular vein. There was no clear site of primary malignancy on radiographic imaging or office nasopharyngolaryngoscopy.

Direct laryngoscopy, bronchoscopy, and tonsillectomy with biopsies of the left base of tongue, glosso-tonsillar sulcus, and left tonsil were negative for malignancy. Fine needle aspiration showed squamous cell carcinoma, HPV, p16, and EBV testing were not performed. The final diagnosis was unknown primary squamous cell carcinoma of the head and neck.

The patient received intensity-modulated radiation therapy (IMRT) with 70 Gy prescribed to the gross tumor volume (PTV HR) and 56 Gy to the oropharynx, nasopharynx, and bilateral lymphatics (PTV SR) in 35 daily fractions (Fig. 1). The left brachial plexus received a mean dose of 44 Gy, a max dose of 56 to 0.1 cc, and a max point dose of 57 Gy. He also received three cycles of concurrent cisplatin at 100 mg/m^2. Daily cone-beam CT was used for radiotherapy image guidance. The patient experienced expected acute/subacute treatment toxicities including percutaneous endoscopic gastrostomy placement at 44 Gy, which was removed post-therapy.

Fifteen months following therapy completion, the patient endorsed left neck pain that radiated to his anterior left shoulder, axilla, and arm limiting its use. He had 5/5 strength and no paresthesias. MRI of the left brachial plexus was performed revealing enhancement and inflammation (Fig. 2). The case and imaging was discussed at this institution's multidisciplinary head and neck tumor board with consensus that symptoms were likely representative of RIBP. Dexamtheasone was prescribed for 2 weeks, pentoxifylline and vitamin E for 6 months, and HBO.

The patient returned for follow-up 2 months later after completing 30 dives of HBO at 2.4 atmospheres for 2 hours per session. He developed an adverse reaction to the vitamin E and trental and only completed 10 days of medication. He reported pain resolution and full range of motion of his left arm. Physical exam showed no signs of brachial plexopathy and normal (pre-radiation treatment quality) sensation, strength, and range of motion of his left arm. Follow-up brachial plexus MRI, six months after the initial MRI, revealed significantly decreased abnormal enhancement compared to prior (Fig. 2). At 13 months out from HBO, he has had no reoccurrence of RIBP symptoms.

3. Discussion

RIBP results from delayed damage to mature nerve tissue secondary to microvascular injury and radiation-induced fibrosis and is most commonly seen in patients treated with radiotherapy for breast and head and neck cancer.[12] Chen et al. published the largest study on RIBP in the setting of high-dose radiation for head and neck cancer (n = 330) and found a 22% incidence of RIBP at 5 years post-treatment and Powell et al. reported a 5% incidence at 5.5 years in the largest published series on RIBP in the breast cancer population (n = 449).[2,13] As the total dose of radiation received in head and neck cancer is typically higher than breast cancer, it is expected to see a higher frequency of RIBP in this population.

The most important predictor of RIBP is biological effective dose, including total dose and fraction size. Currently, the Radiation Therapy Oncology Group (RTOG) recommends the dose to the brachial plexus be below 60–66 Gy. Chen et al. reported on 40 patients with RIBP associated symptoms.[13,14] Patients who received >70 Gy to the brachial plexus developed RIBP at a higher frequency than lower doses. However, the development of RIBP in patients who received <60 Gy to the brachial plexus was not zero, suggesting that RIBP is multifactorial and not solely based on dose.[13]

Current RIBP treatment centers on symptom management. Corticosteroids are used to combat symptoms. Non-opioid analgesics, benzodiazepines, tricyclic antidepressants, and anti-epileptics can treat associated pain.[5] Surgical methods including neurolysis, omentoplasy, and pedicle graft of the latissimus dorsi muscle have had variable efficacy.[15] Another

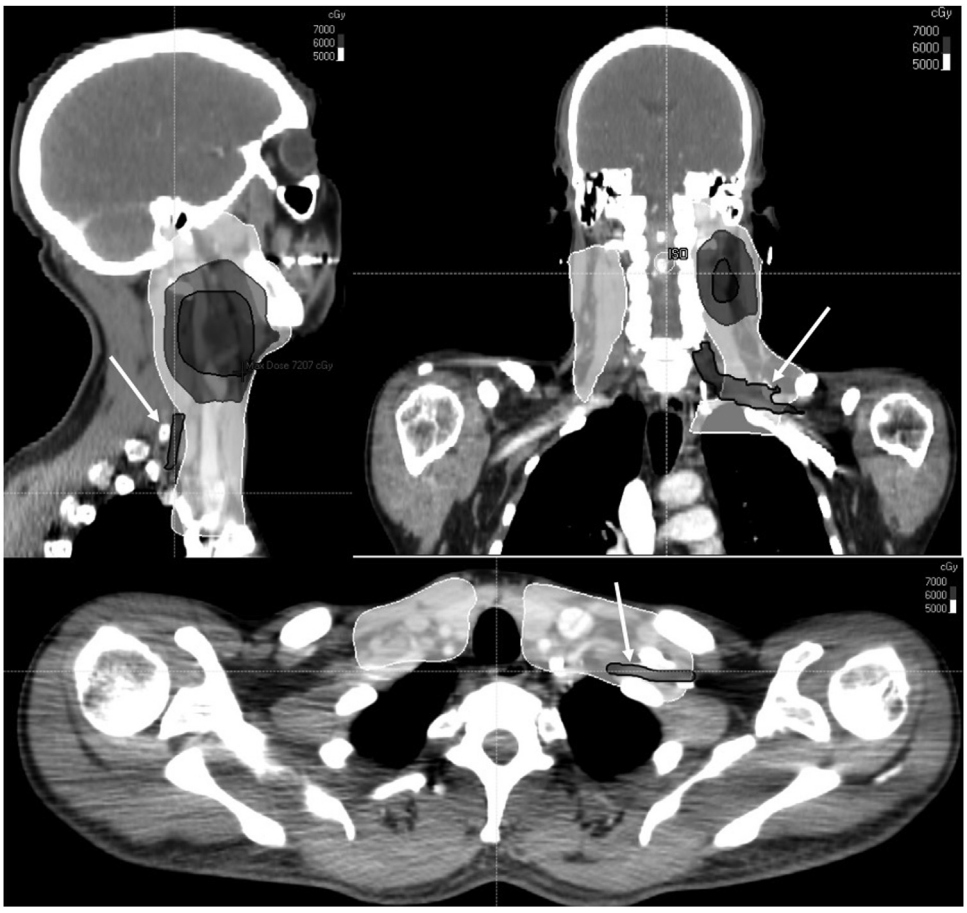

Fig. 1 – Radiation Treatment Plan (IMRT – 70 Gy in 35 fractions).
***Contoured location of brachial plexus depicted by arrow. Isodose Lines: 70 Gy in black, 60 Gy in gray, 50 Gy in white.**

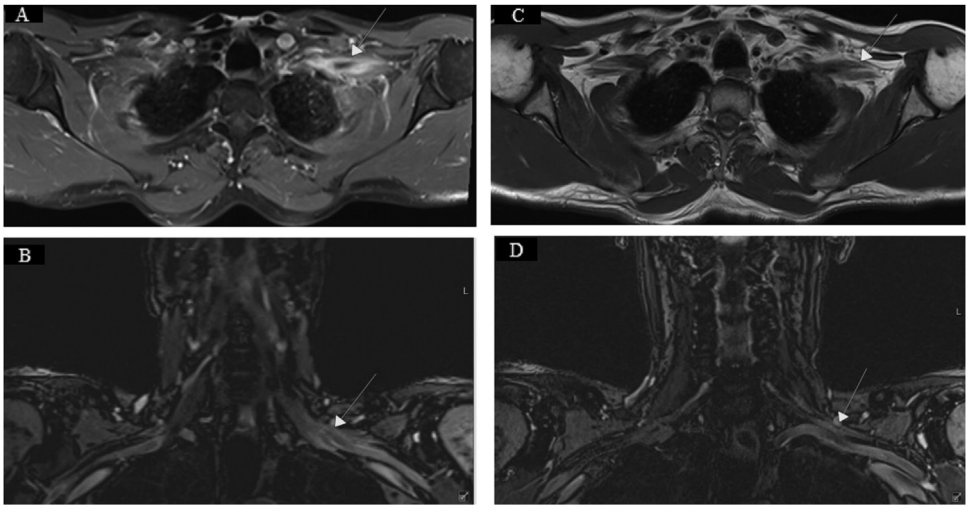

Fig. 2 – (A & B) Pre-HBO therapy axial and coronal MRI of the left brachial plexus. MRI reveals abnormal ill-defined enhancement surrounding the left brachial plexus at the level of the proximal and mid-left clavicle. (C & D) Post-HBO therapy axial and coronal MRI of the left brachial plexus revealing treatment response with significantly decreased abnormal enhancement compared to prior pre-treatment MRI.

possible option is HBO therapy. HBO causes oxygen tension to rise to normal levels enabling fibroblast proliferation, collagen formation, and angiogenesis thus improving vascular density and oxygenation.[16] Delayed radiation injury is one of the Undersea and Hyperbaric Medical Society approved indications for HBO therapy.[17] Evidence supports HBO therapy in various late term sequelae of radiotherapy including mandibular osteoradionecrosis, refractory hemorrhagic cystitis, and vaginal vault and perineal necrosis.[18–22] However, evidence in support of HBO therapy in RIBP is limited and inconsistent. A double-blind, placebo-controlled, randomized trial of 34 patients with RIBP showed no evidence that HBO slowed or reversed RIBP.[23] Eligible patients were those with confirmed RIBP, freedom from cancer recurrence, and physical and psychological fitness for HBO. Patients had varying severity, duration, and timing of RIBP (i.e. heterogenous cohort of patients enrolled). Patients with complete arm paralysis were ineligible. Due to the small number of patients, the study may have been underpowered. Patients in this study received a similar course of HBO as our patient (2.4 atm for 30 total treatments), but received less treatment time per session (100 minutes versus 120 minutes). There are other reports that demonstrate improvement in sensory and motor function with the use of HBO therapy.[24–26]

Despite meeting recommended dose constraints, our patient developed symptoms within 15 months of radiotherapy completion. He may have an inherent hypersensitivity to radiotherapy which led to RIBP despite the low total dose, low dose per fraction, and relatively short follow up period. Another explanation could be the concurrent high dose cisplatin. Chen et al. reported that patients who received concurrent chemotherapy, typically cisplatin, had 2.43 times greater odds of developing RIBP.[13] Our patient had a complete clinical response after HBO therapy, which may be due to early identification and treatment.

4. Conclusions

The best management strategy of RIBP is prevention by reducing total RT doses, limiting the amount of radiation per fraction, and restricting the total point dose to the brachial plexus to <66 Gy for head and neck patients and <60 Gy for breast patients. We also recommend close follow-up for at-risk patients for early diagnosis and treatment with HBO therapy, steroids, trental, and vitamin E as tolerable.

Conflict of interest

None declared.

Financial disclosure

None declared.

Informed consent

Informed consent was obtained from the patient to be a part of this manuscript.

REFERENCES

1. Mondrup K, Olsen NK, Pfeiffer P, Rose C. Clinical and electrodiagnostic findings in breast cancer patients with radiation-induced brachial plexus neuropathy. *Acta Neurologica Scandinavica* 2009;**81**(2):153–8, http://dx.doi.org/10.1111/j.1600-0404.1990.tb00952.x.
2. Powell S, Cooke J, Parsons C. Radiation-induced brachial plexus injury: follow-up of two different fractionation schedules. *Radiother Oncol* 1990;**18**(3):213–20, http://dx.doi.org/10.1016/0167-8140(90)90057-4.
3. Olsen NK, Pfeiffer P, Johannsen L, Schrøder H, Rose C. Radiation-induced brachial plexopathy: neurological follow-up in 161 recurrence-free breast cancer patients. *Int J Radiat Oncol Biol Phys* 1993;**26**(1):43–9, http://dx.doi.org/10.1016/0360-3016(93)90171-q.
4. Bentzen SM, Thames HD, Travis EL, et al. Direct estimation of latent time for radiation injury in late-responding normal tissues: gut, lung, and spinal cord. *Int J Radiat Biol* 1989;**55**(1):27–43, http://dx.doi.org/10.1080/09553008914550041.
5. Delanian S, Lefaix J-L, Pradat P-F. Radiation-induced neuropathy in cancer survivors. *Radiother Oncol* 2012;**105**(3):273–82, http://dx.doi.org/10.1016/j.radonc.2012.10.012.
6. Killer HE, Hess K. Natural history of radiation-induced brachial plexopathy compared with surgically treated patients. *J Neurol* 1990;**237**(4):247–50, http://dx.doi.org/10.1007/bf00314628.
7. van Es HW, Engelen AM, Witkamp TD, Ramos LMP, Feldberg MAM. Radiation-induced brachial plexopathy: MR imaging. *Skeletal Radiol* 1997;**26**(5):284–8, http://dx.doi.org/10.1007/s002560050236.
8. Glazer HS, Lee JK, Levitt RG, et al. Radiation fibrosis: differentiation from recurrent tumor by MR imaging. *Radiology* 1985;**156**(3):721–6, http://dx.doi.org/10.1148/radiology.156.3.4023233.
9. Ebner F, Kressel HY, Mintz MC, et al. Tumor recurrence versus fibrosis in the female pelvis: differentiation with MR imaging at 1.5 T. *Radiology* 1988;**166**(2):333–40, http://dx.doi.org/10.1148/radiology.166.2.3422025.
10. Portenoy RK, Lesage P. Management of cancer pain. *Lancet* 1999;**353**(9165):1695–700, http://dx.doi.org/10.1016/s0140-6736(99)01310-0.
11. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. *Surgery* 1981;**90**(2):262–70.
12. Cavanagh JB. Effects of X-irradiation on the proliferation of cells in peripheral nerve during allerian degeneration in the rat. *Br J Radiol* 1968;**41**(484):275–81, http://dx.doi.org/10.1259/0007-1285-41-484-275.
13. Chen AM, Hall WH, Li J, et al. Brachial plexus-associated neuropathy after high-dose radiation therapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2012;**84**(1):165–9, http://dx.doi.org/10.1016/j.ijrobp.2011.11.019.
14. Fowble BL, Solin LJ, Schultz DJ, Goodman RL. Ten year results of conservative surgery and irradiation for stage I and II breast cancer. *Int J Radiat Oncol Biol Phys* 1991;**21**(2):269–77, http://dx.doi.org/10.1016/0360-3016(91)90771-u.
15. Narakas AO. Operative treatment for radiation-induced and metastatic brachial plexopathy in 45 cases, 15 having an omentoplasty. *Bull Hospital Jt Dis Orthop Inst* 1984;**44**(2):354–75.
16. Greenwood TW, Gilchrist AG. Hyperbaric oxygen and wound healing in post-irradiation head and neck surgery. *Br J Surg* 1973;**60**(5):394–7, http://dx.doi.org/10.1002/bjs.1800600522.

17. Hampson Neil B. Hyperbaric oxygen therapy: 1999 committee report. In: *Undersea and Hyperbaric Medical Society.*; 1999.
18. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dental Assoc* 1985;**111**(1):49–54, http://dx.doi.org/10.14219/jada.archive.1985.0074.
19. Mounsey RA, Brown DH, O'Dwyer TE, Gullane PJ, Koch GH. Role of hyperbaric oxygen therapy in the management of mandibular osteoradionecrosis. *Laryngoscope* 1993;**103**(6):605–8, http://dx.doi.org/10.1288/00005537-199306000-00005.
20. Bevers RF, Kurth K, Bakker D. Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. *Lancet* 1995;**346**(8978):803–5, http://dx.doi.org/10.1016/s0140-6736(95)91620-2.
21. Lee HC, Liu CS, Chiao C, Lin SN. Hyperbaric oxygen therapy in hemorrhagic radiation cystitis: a report of 20 cases. *Undersea Hyperb Med* 1994;**21**(3):321–7.
22. Williams Jr JA, Clarke D, Dennis WA, Dennis III EJ, Smith ST. The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. *Am J Obstet Gynecol* 1992;**167**(2):412–6, http://dx.doi.org/10.1016/s0002-9378(11)91421-5.
23. Pritchard J, Anand P, Broome J, et al. Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiother Oncol* 2001;**58**(3):279–86, http://dx.doi.org/10.1016/s0167-8140(00)00319-4.
24. Videtic GMM, Venkatesan VM. Hyperbaric oxygen corrects sacral plexopathy due to osteoradionecrosis appearing 15 years after pelvic irradiation. *Clin Oncol* 1999;**11**(3):198–9, http://dx.doi.org/10.1053/clon.1999.9043.
25. Hary GB, Mainous EG. The treatment of radiation necrosis with hyperbaric oxygen (OHP). *Cancer* 1976;**37**(6):2580–5, http://dx.doi.org/10.1002/1097-0142(197606)37:6<2580::aid-cncr2820370603>3.0.co;2-h.
26. Glassburn JR, Brady LW. Treatment with hyperbaric oxygen for radiation myelitis. *Proc. 6th Int Cong on Hyperbaric Medicine* 1977:266–77.