Chondroradionecrosis of Larynx a Delayed Complication of Radiotherapy: Management and Review of Literature

Rajshekar Halkud · Ashok M. Shenoy · Sudhir M. Naik ·
Tanveer Pasha · Purshottam Chavan · K. T. Sidappa

Received: 22 August 2013 / Accepted: 13 May 2014 / Published online: 23 May 2014
© Indian Association of Surgical Oncology 2014

Abstract Background/objectives Chondroradionecrosis (CRN) of the larynx is a rare and grave complication of radiotherapy which can be fatal if not managed aggressively. A recent trend towards organ preservation protocols towards even advanced stage laryngeal malignancies and with further advances in terms of technology and safety radiation as external beam and intensity modulated varieties are preferred for certain stages of squamous cell carcinomas. Materials and methods We are reporting a series of 4 cases of CRN of the larynx treated in our hospital with 3 cases of stage III carcinoma glottis and one stage III carcinoma supraglottis with no nodal metastasis. One glottis cancer had 2 sittings of laser microlaryngeal excision earlier. All were in grade 4 CRN and one improved with medical line and HBO and the other 3 progressed and salvage laryngectomy and pectoralis major myocutaneous flap to cover the fistulous skin defect was grafted. Conclusion: Laryngeal CRN being a rare and intensely morbid complication of radiotherapy should be suspected and diagnosed at the earliest by endoscopic and imaging methods. Disease progression and chances of tumor recurrence should be followed up with PET CT and a call on salvage laryngectomy with repair of the anterior neck defects with non irradiated musculocutaneous flaps or vascularised tissue transfer should be promptly taken.

Keyword Chondroradionecrosis · Radiotherapy · Hyperbaric oxygen therapy · Aryngectomy

R. Halkud · A. M. Shenoy · S. M. Naik (✉) · P. Chavan ·
K. T. Sidappa
Department of Head and Neck oncosurgery, KMIO, Bangalore,
Karnataka, India
e-mail: sud223@gmail.com

T. Pasha
Department of Radiation oncology, KMIO, Bangalore, Karnataka,
India

Introduction

Chondroradionecrosis (CRN) of the larynx is a rare and grave complication of radiotherapy which can be fatal if not managed aggressively.¹ Laryngeal cancers have been treated radically with radiation for the past seven decades.¹ A recent trend towards organ preservation protocols towards even advanced stage laryngeal malignancies and with further advances in terms of technology and safety radiation as external beam and intensity modulated varieties are preferred for certain stages of squamous cell carcinomas.¹

This modality of treatment has also bound complications like as laryngeal edema, skin damage, perichondritis and rarely cartilage necrosis.¹

CRN is a late complication of radical radiotherapy with minimal incidences ranging below 1 % and a higher incidence is expected in the era of concomitant chemoradiotherapy.^{2,3} As it's a rare complication and with proven fatality early detection with endoscopic and imaging with pathologic confirmation to rule out recurrence should be initiated.¹

Apart from radiation chondronecrosis can also be caused by recurrent perichondritis, long- or short-term intubations, infection, trauma, tracheotomy and the malignancy itself.¹ Recent advances in radiation therapy like the conformal and the intensity modulated techniques managing SCC of the larynx have become safer and effective with minimal collateral damage and functionality with oncological control.¹

As a result complications rate dropped from 5 to 12 % to below 1 % over three decades.¹ The incidence of severe reactions following 50–60 Gy had decreased from 5 to 12 %, in the 1970s, to approximately 1 %, in the 1990s.⁴ An hypoxic induced by reactive fibrosis and end-arteritis of blood vessels, as well as obliteration and fibrosis of the lymphatic system depending on tumor stage and radiation dose.⁴ Congestion results due to increased permeability and decreased lymphatic drainage, which leads to increased

hypoxia and chondronecrosis.⁴ So an early diagnosis of the CRN with debridement of the necrotic tissue and hyperbaric oxygen therapy may improve and save the functional larynx.⁴.

Materials and methods

We are reporting a series of 4 cases of CRN of the larynx treated in our hospital during the study period between jan 2009 to June 2013. All the 4 were males in the study with an average age of 60.75 years with 3 cases of stage III carcinoma glottis and one stage III carcinoma supraglottis with no neck nodes seen. One glottis cancer had 2 sittings of laser microlaryngeal excision earlier. All the 4 were seen in the department and as they were in the stages III, they were referred to radiation therapy. All the 3 cases of glottis cancers were treated with external beam RT of 70 grays and the other supraglottic case was also given external beam RT of 70 grays with cisplatin 100 mg/m² body surface area.(table 1).

All presented with pain at the irradiated site, hoarseness and stridor. Indirect laryngoscopy done revealed edematous cords with restricted mobility suggestive of submucosal recurrence, emergency tracheostomy was done in all the cases to relieve stridor. Routine blood and urine investigations, thyroid profile were done and no hypothyroidism was seen in all the 4 cases.

CT scan of the larynx and hypopharynx done showed diffuse irregular thickening of true and false cords on right side with extension across anterior commissure to opposite side, irregular soft tissue lesion was also seen infiltrating the pre epiglottic and paraglottic space suggestive of recurrence.(fig 1).

Direct laryngoscopy done under general anaesthesia confirmed the clinical and radiological features and biopsy was taken from suspicious areas to rule out recurrence, however it turned out to be negative. Among the 4 patients 2 obliged for 32 dives of hyper baric oxygen therapy (HBO). Symptomatic improvement was seen in one case and the other three has persistent pain at the site. PET CT was done in the 3 cases which suggested suspicious uptake at the specific areas. The patient (taken HBO) who had dramatic improvement was discharged with advice for tracheostomy care and follow up every 3 months with nutritional supplementation.

The other 3 cases has progression of laryngeal tenderness with the CRN not settling, the patients were planned for salvage laryngectomy as the laryngeal function was compromised. The functional compromise was explained to the patient attenders and an informed written consent was taken explaining them the possibility of negative histopathology post operatively.(fig 2) The salvage surgery which included narrow field laryngectomy, excision of involved skin in the neck and primary closure of neopharynx with pectoralis major myocutaneous flap repair for the skin defect.(fig 3) The post-

Table 1 summary of the patients with their management and outcome

no	Sex	age	Tumor stage	Earlier treatment	Radical RT dose	Time to CRN	symptoms	signs	Subsite	grade	treatment	HBO dives	Biopsy proven or not	Tumor recurrence	outcome
1	m	56	T3N0M0 glottis	nil	70 gy	8	Pain, hoarseness stridor	Erosion, fistula, edema	thyroid cartilage cricoid cartilage	IV	Antibiotics, Nutrition, HBO	32	(-)	PET (-)	Improved
2	m	58	T3N0M0 glottis	nil	70 gy	9	Pain, hoarseness stridor	Erosion, fistula, edema	thyroid cartilage cricoid cartilage	IV	Antibiotics, Nutrition, HBO	-	(-)	PET (-)	TL, PMMC
3	m	61	T3N0M0 glottis	2 sittings LASER MLE	70 gy	6	Pain, hoarseness stridor	Erosion, fistula, edema	thyroid cartilage cricoid cartilage	IV	Antibiotics, Nutrition, HBO	-	(-)	PET (-)	TL, PMMC
4	m	68	T3N0M0 supraglottis	nil	70 gy	7	Pain, hoarseness stridor	Erosion, fistula, edema	thyroid cartilage cricoid cartilage	IV	Antibiotics, Nutrition, HBO	32	(-)	PET (-)	TL, PMMC

Fig. 1 Coronal sections showing collapse of the laryngeal framework

operative period in all the 3 cases were uneventful with no evidence of any recurrent tumor. The laryngeal cartilage showed necrosis with inflammatory cell infiltration around it and diagnosis of CRN was confirmed. All the 3 were discharged with no further complication.

Discussion

Laryngeal CRN being a rare serious complication of radiotherapy are being reported more with the increased use of concomitant chemoradiotherapy. ² CRN should be suspected when complaints of increased hoarseness, dryness, severe pain and edema, respiratory distress, fetor oris and fistula formation after

radical radiotherapy of 70 grays and more.⁵ These features are similar to recurrent tumors which should be excluded by imaging.^{4,6,7} CRN of larynx usually complicates prognosis within the first year of radiotherapy but may occur more than 10 years also.^{8,9} Continuing smoking and tobacco, tumor recurrence, post-operative infection, trauma, and the radiation technique and dosage are all risk factors for CRN of larynx.¹

Irradiation induced vasculitis narrowing and occluding the intravascular lumen and lymphatics leads to an obliteration, atrophy and fibrosis of the laryngeal perichondrium.⁸ Factors such as initial integrity of the cartilage, underestimated initial tumor infiltration, previous surgical intervention, and infection, can promote CRN as the intact perichondrium can tolerate large doses of radiation.^{2,10}

Fig. 2 Total laryngectomy with excision of the fistulous skin

Fig. 3 Pectoralis major myocutaneous flap covering the skin defect after primary pharyngeal closure

CRN being a late major complication typically occurs after a latent period of 3–4 months due to prolonged hypovascularity resulting in lowering of resistance and reparative capacity of the irradiated tissue.¹¹ As the incidence range from 1 to 5 % laryngeal edema due to radiation may mask the initial stages of CRN.¹ The edema is proportional to the radiation dosage, field, volume of tissue radiated, addition of neck dissection and size and extent of the original lesion and seen in 13.7 % of patients who receive a dose less than 70 Gy but rises to 46.2 % with doses of 70 Gy or more.¹

CRN leads to defective and unstable cartilaginous framework which alters the airway size, mobility and structure.¹ Arytenoid cartilages is affected earlier with partially fixing the crico-arytenoid joint.¹ Hoarseness and stridor progresses as due to vocal cord fixation increases and often aspiration is encountered.¹ Initial dysphagia to liquids which progresses to solids as the accessory laryngeal muscle activity are impaired due to fibrosis, impairing the normal laryngeal elevation needed for swallowing while opening up an unprotected airway.¹

CRN manifests within the first 3 months after radiotherapy but reports of a delay of 25, 44 and even 50 years are seen in literature.^{10,12} Functional compromise as aspiration and recurrent pneumonia warrants surgical removal of the larynx.² The typical patient with CRN larynx initially develops symptoms of hoarseness and stridor and the incidence is directly related to quantity of radiation delivered and the severity of the subsequent reaction.^{1,5}

Chandler classified laryngeal CRN into 4 grades with minimal to moderate hoarseness and dryness seen in the initial 2 grades.¹³ As slight edema and telangiectasia were seen in these two grades symptomatic treatment with anti-GERD, humidification, nutritional, complete voice rest and strict

smoking cessation with imaging to rule out recurrence were advised.¹³

Severe hoarseness, dyspnea with moderate odynophagia and dysphagia were seen in Grade 3 and signs of severe impairment of vocal cord mobility or fixation of one cord, marked oedema, skin changes were present.¹³ Admission, symptomatic care, steroids, and antibiotics with emergency tracheostomy if needed marks the protocol.¹³ Grade 4 marks emergency with severe respiratory distress, odynophagia, weight loss and dehydration with fistula formation, fetor oris, fixation of skin to larynx, airway obstruction and fever.¹³ Emergency securing the airway with tracheostomy with all the above supportive measures and laryngectomy as the emergency settles should be done here.¹³

Although CRN is diagnosed clinically, both CT and MRI are not confirmatory in distinguishing between radio-necrosis and recurrent tumour.^{2,12} Contrast enhanced Computerised tomography (CECT) of the larynx is nonspecific and indistinguishable from that of tumor recurrence.¹⁴ CRN, features as sloughing of the arytenoid cartilage, fragmentation and collapse of the thyroid cartilage or the presence of gas bubbles around the cartilage in only half of the cases.^{7,14} Mixed features of enhanced and non-enhanced lesions at both the epiglottis and thyroid cartilage levels can be mistaken for tumor recurrence.⁹ Direct laryngoscopy and biopsy of these submucosal recurrent lesions may yield negative results with ambiguity seen on CECT larynx.⁹ Recurrence may lead onto CRN where diagnosis is extremely difficult.⁹

Early radiation changes, CRN and tumor recurrence can be differentially imaged by Fludeoxyglucose- Positron emission tomography- (FDG-PET CT).⁹ It can predict recurrence 3 months postirradiation, and can distinguish CRN and recurrence in the irradiated larynx but a laryngoscopic biopsy is

needed to prove it.^{4,15} As many submucosal biopsies are negative despite PET positivity deeper multiple smaller punches are advised.^{4,7} Its better to do PET-CT in grade III/IV looking for recurrence and followed by biopsy in PET-positive patients.⁶ Also the patients may be followed up with PET CT if the biopsies are negative and a decreased uptake may favour CRN.¹⁵ Also the resolution of PET-CT is 6 mm with the microscopic deposits being missed and the larger one masked by saliva.²

McGuirt et al. reported 80 % accuracy of differentiating the tumor recurrence from CRN using PET-CT.⁶ Roh J-L et al. reported false-positive PET results in one case out of his six cases while none having recurrence on biopsy and suggested PET CT to be beneficial in decision making in tumor recurrence in cases of laryngeal CRN.¹ Lederman et al. in 1972 outlined the 4 main complications of radiotherapy to the larynx i.e., laryngeal edema, skin damage, perichondritis and necrosis.¹⁶

Keene et al., studied 265 laryngeal specimens received after eradication of primary squamous cell carcinoma noted histologic chondronecrosis in 26 % and only 3 % of them were clinically diagnosed to have laryngeal chondronecrosis.⁹ Zbaren et al. reported in his retrospective study of 341 patients with laryngeal or hypopharyngeal carcinomas treated with radiotherapy alone or with chemoradiotherapy that 4 (1.2 %) had CRN, and 8 (2.3 %) had both CRN and tumor recurrence.⁷ Fitzgerald PJ et al. reported the longest interval of development of laryngeal CRN 50 years after irradiating a patient with early glottis cancer.¹² Reports of CRN in patients being irradiated after post laser microlaryngeal excision indicates laryngeal subsites previously injured by laser surgery may be more vulnerable to irradiation injury, resulting in cartilage exposure and necrosis.¹

Hyperbaric oxygen therapy (HBO) used to treat radiation necrosis of the head and neck helps to repair vascular beds within the irradiated tissue, enhancing neovascularization and wound healing.^{8,17–19} Filntis et al., retrospectively evaluated 18 patients; 13 (72 %) showed functional and symptomatic improvement, 4 failed to respond to treatment, and 1 developed recurrence.⁸ In the study 2 had grade 3 and 16 cases were of grade 4 CRN treated with HBO showed major improvement and none of them required total laryngectomy.⁸

HBO can eliminate laryngectomies and even enable tracheostomies to be decannulated but a large randomized controlled studies of HBO in the treatment of CRN is not possible due to rarity of the condition.^{8,19,20} They also reported early removal of necrotic tissue under suspension laryngoscopy may be helpful in the treatment of CRN, in combination with HBO. Ferguson et al., reported drastic clinical improvement in 7 out of the 8 patients of grade 3 and 4 patients treated with HBO.¹⁹

Total laryngectomy is preferred in progressive CRN, non-functional larynx, and a high suspicion of tumor recurrence.¹ Medical management including HBO in progressive CRN is only symptomatic and surgical treatment is needed in grade 3

and grade 4 cases.⁸ Pathological process is not well defined as to how the aseptic necroses start and what limits the necrosis and so surgical margins differ from the routine cases of salvage laryngectomies.⁸ Under anaesthesia laryngeal endoscopic biopsy with frozen section should be done to confirm the diagnosis.⁸

Cukurova et al., described debridement of the necrotic tissues at the first sitting with fragments of the affected cartilages being removed to promote healing.¹³ Salvage laryngectomy can be deferred by removing necrotic cartilage and allowing secondary wound healing.¹³ They advised salvage surgery if the CRN progresses at a second stage with a pectoralis major myocutaneous flap (PMMC) from a nonradiated site used for closing the fistula.¹³ The PMMC flap supplied by thoraco-acromial artery, with additional circulation provided by the lateral thoracic artery is an accepted workhorse in head and neck cancer reconstructions.²¹

Conclusion

Laryngeal CRN being a rare and intensely morbid complication of radiotherapy should be suspected and diagnosed at the earliest by endoscopic and imaging methods. As pathological confirmation is needed for tumor recurrence an early debridement, HBO and aggressive medical line may help save the functional larynx.

Disease progression and chances of tumor recurrence should be followed up with PET CT and a call on salvage laryngectomy with repair of the anterior neck defects with non irradiated musculocutaneous flaps or vascularised tissue transfer should be promptly taken.

References

1. Jong-Lyel Roh: Chondroradionecrosis of the Larynx: and Therapeutic Measures for Saving the Organ from Radiotherapy Sequelae: Clinical and Experimental Otorhinolaryngology Vol. 2, No. 3: 115–119, September 2009.
2. Oppenheimer RW, Krespi YP, Einhorn RK. Management of laryngeal radionecrosis: animal and clinical experience. *Head Neck*. 1989 May-Jun;11 (3):252–6.
3. Stell PM, Morrison MD (1973) Radiation Necrosis of the Larynx: Etiology and Management. *Arch Otolaryngol* 98:111–113
4. Rowley H, Walsh M, McShane D et al (1995) Chondroradionecrosis of the Larynx: Still a Diagnostic Dilemma. *J Laryngol Otol* 109:218–20
5. Chandler JR. Radiation fibrosis and necrosis of the larynx. *Ann Otol Rhinol Laryngol*. 1979 Jul-Aug;88 (4 Pt 1):509–14.
6. McGuirt WF, Greven K, Williams D 3rd et al (1998) PET Scanning in Head and Neck Oncology: A Review. *Head Neck* 20:208–15
7. Zbaren P, Caversaccio M, Thoeny HC, Nuyens M, Curschmann J, Stauffer E (2006) Radionecrosis or Tumor Recurrence After Radiation of Laryngeal and Hypopharyngeal Carcinomas. *Otolaryngol Head Neck Surg* 135(6):838–43

8. Filntis GA, Moon RE, Kraft KL, Farmer JC, Scher RL, Piantadosi CA (2000) Laryngeal Radionecrosis and Hyperbaric Oxygen Therapy: Report of 18 Cases and Review of the Literature. *Ann Otol Rhinol Laryngol* 109: 554–562
9. Keene M, Harwood AR, Bryce DP, Peter van, Nostrand AW. Histopathological study of radionecrosis in laryngeal carcinoma. *Laryngoscope* 1982;92:173–80
10. Baba Y, Kato Y, Ogawa K (2011) Unusual Computed Tomography Findings of Radionecrosis After Chemoradiation of Stage IV Hypopharyngeal Cancer: A Case Report. *Journal of Medical Case Reports* 5:25
11. Takiguchi Y, Okamura HO, Kitamura K et al (2003) Late Laryngotracheal Cartilage Necrosis With External Fistula 44 Years After Radiotherapy. *J Laryngol Otol* 117:658–9
12. Fitzgerald PJ, Koch RJ (1999) Delayed Radionecrosis of the Larynx. *Am J Otolaryngol* 20:245–9
13. Cukurova EA (2010) Cetinkaya. Radionecrosis of the Larynx: Case Report and Review of the Literature. *Acta Otorhinolaryngologica Italica* 30:205–208
14. Hermans R, Pameijer FA, Mancuso AA, Parsons JT, Mendenhall WM (1998) CT Findings in Chondroradionecrosis of the Larynx. *AJNR Am J Neuroradiol* 19(4):711–8
15. Greven KM, Williams DW 3rd, Keyes JW Jr, McGuirt WF, Harkness BA, Watson NE Jr et al (1994) Distinguishing Tumor Recurrence from Irradiation Sequelae With Positron Emission Tomography in Patients Treated for Larynx Cancer. *Int J Radiat Oncol Biol Phys* 29(4):841–5
16. Lederman M (1972) Radiation Therapy in Cancer of the Larynx. *JAMA* 221(11):1253–4
17. Greenwood TW, Gilchrist AG (1973) Hyperbaric Oxygen and Wound Healing in Post-Irradiation Head and Neck Surgery. *Br J Surg* 60(5):394–7
18. Hao SP, Chen HC, Wei FC, Chen CY, Yeh AR, Su JL (1999) Systematic Management of Osteoradionecrosis in the Head and Neck. *Laryngoscope* 109(8):1324–7
19. Ferguson BJ, Hudson WR, Farmer JC Jr. Hyperbaric oxygen therapy for laryngeal radionecrosis. *Ann Otol Rhinol Laryngol.* 1987 Jan-Feb; 96 (1 Pt 1):1–6.
20. Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ (1993) Hyperbaric Oxygen as an Adjunctive Treatment for Severe Laryngeal Necrosis: A Report of Nine Consecutive Cases. *Undersea Hyperb Med* 20(4):329–35
21. Dedivitis RA, Guimaraes AV (2002) Pectoralis Major Musculocutaneous Flap in Head and Neck Cancer Reconstruction. *World J Surg* 26:67–71