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Laryngeal necrosis after combined chemotherapy and radiation therapy

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Abstract
Post-radiation necrosis of the larynx is a major complication after irradiation and has become rare. Recently, combined chemotherapy and radiation therapy has been introduced for head and neck tumours. The authors report a case of laryngeal necrosis after combination therapy for a patient with cervical lymph node metastases of nasopharyngeal carcinoma and review the literature on late laryngeal necrosis. Although radiation-induced laryngeal necrosis has become a rare complication, the combination of chemotherapy and radiation therapy may increase its incidence. We should always consider it as a possible late complication and treat it appropriately.

Key words: Laryngeal cartilages; Necrosis; Radiotherapy; Chemotherapy

Introduction

Irradiation fields including the larynx are used for laryngeal, hypopharyngeal, upper oesophageal carcinomas and cervical lymph node metastases from any primary site. A major complication after irradiation is post-radiation necrosis, most often seen after radiotherapy for laryngeal carcinomas. Suitable doses and fractions have been determined for the use of radiotherapy on the larynx; therefore, the rate of cure by radiotherapy has increased, and its complications have decreased. Post-radiation necrosis of the larynx has become rare. However, a new combination therapy of radiation and anti-cancer drugs may increase its incidence.

In this paper we report a case of laryngeal necrosis after combination therapy for cervical lymph node metastases. We also review the literature on late laryngeal necrosis after irradiation and suggest that this outcome is correlated with the combined use of chemotherapy and radiation therapy.

Case report

In May 1993, a 66-year-male presented with a $T_3N_{2c}M_0$ squamous cell carcinoma of the nasopharynx. He was treated with a combination of radiotherapy and chemotherapy. Radiotherapy consisted of 59.4 Gy in seven weeks, in 33 fractions, with 4 MeV X-rays to the head and neck through alternate lateral ports each day, and a 10 Gy 'boost' in one week, in five fractions, with 6 MeV electron beams to both sides of the neck through lateral ports without any shielding over the larynx. There was little radiation effect observed on the larynx by electron beams through lateral fields. Concomitant with radiotherapy, chemotherapy consisted of cisplatin 10 mg per day twice a week on Monday and Wednesday for 11 injections, and pirarubicin hydrochloride 10 mg once a week on Friday for six injections. The total doses of cisplatin and pirarubicin hydrochloride were 110 mg and 60 mg, respectively. After the radiotherapy was completed, carboplatin (300 mg × one day) and 5-fluorouracil (1,000 mg/body/day × five days) were administered. Complete regression of the tumour was achieved, and mild erosion of the skin of the neck changed to skin pigmentation three months later. In January 1994, the patient complained of high fever and sore throat. Investigation revealed severe laryngeal oedema of the epiglottis and arytenoid regions. He was treated to good effect with antibiotics and steroids. In May 1994, laryngeal oedema appeared again and was treated with similar results. In June 1994, he complained of dyspnoea with dysphagia. A fibrescopic examination showed severe laryngeal oedema, with ulceration of the left arytenoid region and complete immobilization of the bilateral vocal folds. One week later, the ulcerative lesion had disappeared, and the shape of the left arytenoid region had changed. However, a new ulcerative lesion with a white necrotic mass was found in the right arytenoid region (Figure 1), from which biopsies were obtained. Pathological findings were laryngitis without malignant cells. The patient could not eat nor drink because of aspiration and so was fed intravenously. Three weeks later, the ulcerative lesion had healed, and the tubercula of the bilateral arytenoid regions were no longer seen. The vocal folds were completely immobile, with a small slit (Figure 2). Computed tomography (CT) at the level of the vocal folds and their upper and lower levels showed the disappearance of arytenoid cartilages (Figures 3a-c). The patient could speak without dyspnoea but could not eat nor drink because of aspiration. A flexible fibrescope could not be inserted through the pyriform sinus. A barium swallow was attempted on several occasions, but was unsuccessful owing to aspiration. The pyriform sinus and post-cricoid region were almost obstructed by adhesion, and only a small pathway could be seen. Management consisted of permanent gastrostomy without tracheostomy or laryn-

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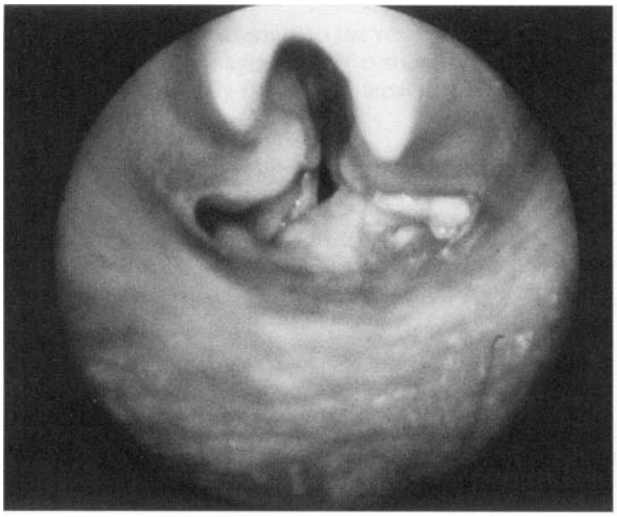

FIG. 1

The tuberculum of the left arytenoid region has disappeared, and a white necrotic mass is seen in the right arytenoid region.

gectomy. CT and magnetic resonance imaging (MRI) one year later revealed no changes. It was confirmed that the laryngeal necrosis had occurred only at the bilateral arytenoid cartilages and had not extended further.

Discussion

At Kagawa Medical School hospital, we had one case with post-radiation laryngeal necrosis out of six patients whose radiation fields included the larynx with combined chemotherapy. Ninety-seven patients receiving more than 60 Gy on the larynx for laryngeal, hypopharyngeal carcinomas, and/or cervical lymph node metastases had been treated by radiotherapy alone. We had never experienced any laryngeal necrosis. Post-radiation laryngeal necrosis has become rare owing to improvements in the radiotherapy technique. Recently, combined chemotherapy and radiation therapy has been introduced for head and neck tumours, and we believe it may increase complications, including laryngeal necrosis.

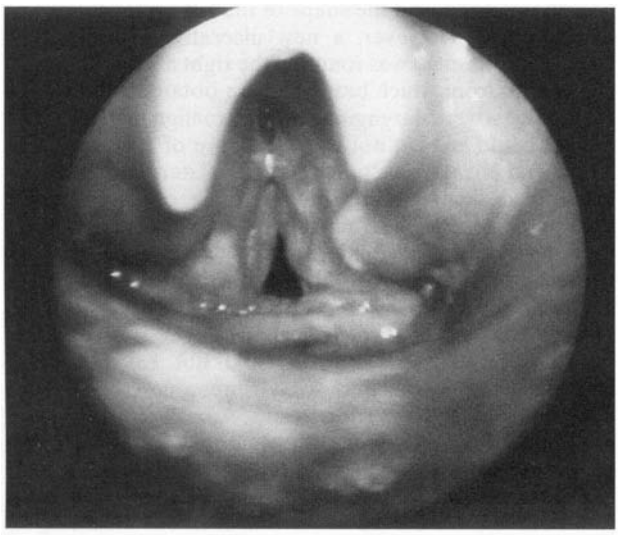

FIG. 2

The tubercula of the bilateral arytenoid region have disappeared, and the bilateral vocal folds are completely immobile, with a small slit.

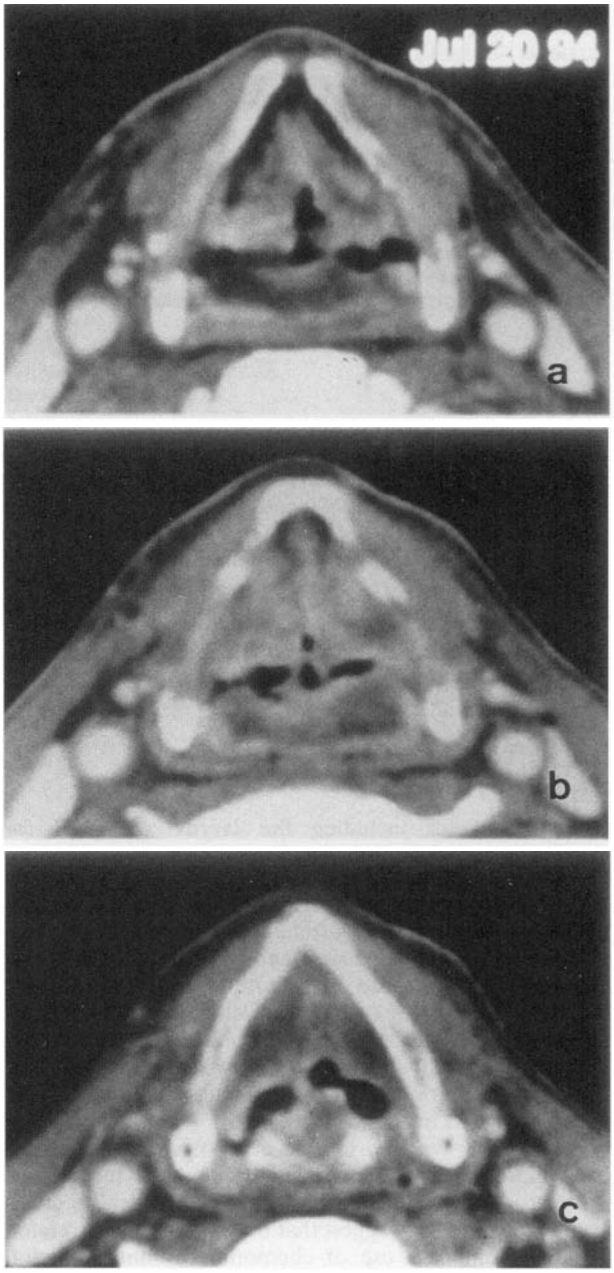

FIG. 3

First CT (on 20 July 1994). a: upper level of vocal folds. b: the level of vocal folds. c: lower level of vocal folds. The bilateral arytenoid cartilages have disappeared, and the upper portion of cricoid cartilage is seen at the lower level of (c).

It is important to know the aetiology of laryngeal necrosis and the way in which chemotherapy affects it. An acute respiratory tract infection may precipitate acute perichondritis some years after irradiation. When the acute perichondritis cannot be treated successfully with antibiotics or steroids, it induces laryngeal necrosis.

Micropathological studies of the reaction of the larynx to radiation were performed by Alexander (1963), Calcaterra *et al.* (1972), Ward *et al.* (1975), Keene *et al.* (1982). The primary change is the dense hyalinization of the acellular perichondrium and the collagen surrounding the capillaries and lymphatic vessels. With this change, the smaller vessels are occluded, and the larger vessels are reduced in calibre, resulting in a marked lowering of the resistance and reparative powers of the irradiated structure (Alexander, 1963). The perichondrium undergoes thicken-

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ing and fibrosis, which reduces the blood supply (Calcaterra *et al.*, 1972). Furthermore, factors that compromise the integrity of the cartilage, such as tumour invasion, infection, or previous surgical intervention, markedly increase the incidence of persistent oedema, which is often the precursor of radiation necrosis (Keene *et al.*, 1982). The arytenoid cartilage is most frequently involved when chondronecrosis occurs in association with radiotherapy (Ward *et al.*, 1975).

The synergistic interaction of a platinum complex and radiation was reported *in vitro* by Chadwick and Leenhouts, 1976. In addition, the work of Byfield *et al.* (1982) suggests that X-rays may sensitize cells to fluorouracil. Because the outcome of chemotherapy or radiotherapy alone has been poor for patients with advanced carcinomas of the head and neck, there has been a strong interest in the combination of chemotherapy and radiotherapy. It seems to represent a substantial improvement in locoregional control and organ preservation, which can maintain the quality of life. Of recent studies with the combination therapy, one case of chrondritis and one case of chondronecrosis of the larynx were reported by Taylor *et al.* (1985), Koch *et al.* (1995), respectively. Because concomitant chemotherapy enhances normal tissue damage (Phillips, 1992), late morbidity of laryngeal necrosis must occur more often after the combination therapy than after radiation alone. Even though the technique of combined chemotherapy and radiotherapy has been improved, the late effect of laryngeal necrosis should be watched for and treated appropriately.

The treatment of laryngeal necrosis consists of antibiotics, with or without steroids, and surgical procedures. The surgical procedures are first, tracheostomy and, second, total laryngectomy. Some trials to avoid total laryngectomy and to preserve laryngeal function have been reported. One of them is the administration of hyperbaric oxygen to improve vascular supply (Hart and Mainous, 1976; Ferguson *et al.*, 1987). The other procedures are new surgical approaches. Oppenheimer *et al.* (1989) reported that submucosal resection of the laryngeal cartilages, leaving the perichondrium and endolaryngeal soft tissue, could result in a competent airway. Balm *et al.* (1993) reported on two patients who underwent excision of the overlying skin and of all infected and devitalized thyroid cartilage, pectoralis major muscle transposition and split-thickness skin grafting. In the case reported here, necrosis of the arytenoid cartilages spontaneously disappeared, following treatment with antibiotics and steroids, and the bilateral arytenoid regions healed well. However, the patient had severe stenosis of the hypopharynx and could not eat nor drink because of aspiration. Therefore, we had to decide whether to preserve speech or swallowing function. Simple total laryngectomy did not seem to be indicated in our patient because of the hypopharyngeal adhesion, so gastrostomy was chosen and speech function was preserved. Although there are many methods available for treating laryngeal necrosis, we should attempt to maintain the highest quality of life, depending on the case.

In conclusion, although radiation-induced laryngeal necrosis has become a rare complication, the combination of chemotherapy and radiotherapy may increase its incidence. We should always consider it as a possible late complication and treat it appropriately.

References

Alexander, F. W. (1963) Micropathology of radiation reaction in the larynx. *Annals of Otology, Rhinology and Laryngology* **72:** 831–841.

Balm, A. J. M., Hilgers, F. J. M., Baris, G., Keus, R. B. (1993) Pectoralis major muscle transposition: an adjunct to laryngeal preservation in severe chondroradionecrosis. *Journal of Laryngology and Otology* **107:** 748–751.

Byfield, J. E., Calabro-Jones, P., Klisak, I., Kulhanian, F. (1982) Pharmacologic requirements for obtaining sensitization of human tumor cells *in vitro* to combined 5-fluorouracil and X rays. *International Journal of Radiation Oncology, Biology and Physics* **8:** 1923–1933.

Calcaterra, T C., Stern, F., Ward, P. H. (1972) Dilemma of delayed radiation injury of the larynx. *Annals of Otology, Rhinology and Laryngology* **81:** 501–502.

Chadwick, K. H., Leenhouts, H. P., Szumiel, I., Nias, A. H. W. (1976) An analysis of the interaction of a platinum complex and radiation with CHO cells using the molecular theory of cell survival. *International Journal of Radiation Biology* **30:** 511–524.

Ferguson, B. J., Hudson, W. R., Farmer, J. C. Jr. (1987) Hyperbaric oxygen therapy for laryngeal radionecrosis. *Annals of Otology, Rhinology and Laryngology* **96:** 1–6.

Hart, C. G. B., Mainous, E. G. (1976) The treatment of radiation necrosis with hyperbaric oxygen (OHP). *Cancer* **37;** 2580–2585.

Keene, M., Harwood, A. R., Bryce, D. P., van Nostrand, A. W. (1982) Histopathological study of radionecrosis in laryngeal carcinoma. *Laryngoscope* **92;** 173–180.

Koch, W. M., Lee, D. J., Eisele, D. W., Miller, D., Poole, M., Cummings, C. W., Forastiere, A. (1995) Chemoradiotherapy for organ preservation in oral and pharyngeal carcinoma. *Archives of Otolaryngology, Head and Neck Surgery* **121:** 974–980.

Oppenheimer, R. W., Krespi, Y. P., Einhorn, R. K. (1989) Management of laryngeal radionecrosis: animal and clinical experience. *Head and Neck* **11:** 252–256.

Phillips, T. L. (1992) Effects of chemotherapy and irradiation on normal tissues. In *Radiotherapy/Chemotherapy Interactions in Cancer Therapy*. 1st Edition. (Meyer, J. L., Vaeth, J. M., eds.) Karger, Basel, pp 45–54.

Taylor, S. G. IV, Murthy, A. K., Showel, J. L., Caldarelli, D. D., Hutchinson, J. C. Jr., Holinger, L. D., Kramer, T., Kiel, K. (1985) Improved control in advanced head and neck cancer with simultaneous radiation and cisplatin/5-FU chemotherapy. *Cancer Treatment Reports* **69:** 933–939.

Ward, P. H., Calcaterra, T. C., Kagan, A. R. (1975) The enigma of post-radiation edema and recurrent or residual carcinoma of the larynx. *Laryngoscope* **85:** 522–529.

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