CASE REPORT

RECURRENT LARYNGEAL CANCER PRESENTING AS DELAYED HYPOPARATHYROIDISM

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Abstract:  Background. Endocrine dysfunction following therapy for head and neck cancer has been previously described. Permanent hypoparathyroidism may result from the tumor, surgery, or radiation therapy. However, the incidence and significance of delayed hypoparathyroidism following treatment for laryngeal cancer remains unclear.

Methods and Results. We report a patient who had stable serum calcium measurements on serial testing following concurrent chemoradiation and salvage laryngectomy for locally advanced laryngeal cancer. The patient subsequently presented 32 months following salvage laryngectomy with new onset, symptomatic hypocalcemia secondary to hypoparathyroidism. Subsequent evaluation revealed local recurrence.

Conclusion. To our knowledge, this case represents the first report of delayed hypoparathyroidism as the presenting manifestation of recurrence following treatment for laryngeal cancer. Possible pathophysiologic mechanisms are discussed.

Keywords: parathyroid; hypoparathyroidism; laryngectomy; hypocalcemia; recurrent cancer

Endocrine dysfunction following therapy for laryngeal cancer has been previously described and may involve the thyroid or parathyroid glands. The reported incidence of hypothyroidism of 65% to 92% following surgery and radiation therapy for laryngeal cancer has resulted in the recommendation for long-term surveillance and therapy.1,2 Although hypoparathyroidism has been similarly reported, its overall incidence remains unclear with reported rates ranging from 0 to 89%.1,3 The incorporation of a hemithyroidectomy or total thyroidectomy as part of the laryngectomy in conjunction with high-dose radiation places this cohort at risk for the occurrence of hypoparathyroidism. However, patients are not routinely followed with long-term serum calcium or parathyroid hormone measurements if the initial postoperative values remain stable. We report a patient with delayed hypoparathyroidism presenting 32 months following concurrent chemoradiation and salvage laryngectomy for advanced laryngeal cancer. This represented the first manifestation of local recurrence and has significant implications for the surveillance of patients who receive multimodality treatment for head and neck cancer.

CASE REPORT

A 64-year-old man with a history of concurrent chemoradiation and salvage laryngectomy for a T4N0M0 transglottic squamous cell carcinoma of
the right true vocal fold presented with new onset, symptomatic hypocalcemia 2.5 years after salvage surgery. The patient completed initial treatment with concurrent external beam radiation therapy consisting of 70 Gy and chemotherapy consisting of 2 cycles of carboplatin and 5-fluorouracil in October 2001. Serum calcium results 1, 6, and 11 months after combined therapy were within normal limits. The patient subsequently presented with laryngeal recurrence and underwent a total laryngectomy, right selective neck dissection (levels II–VI), and right hemithyroidectomy with preservation of the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve in September 2002. The right parathyroid glands were neither dissected nor reimplanted and the left neck and thyroid gland were not dissected. After a brief period of self-limited, asymptomatic hypocalcemia with a corrected serum calcium of 8.1 mg/dL (normal, 8.5–10.5 mg/dL) during the first postoperative week, the patient was normocalcemic. The patient required thyroid hormone replacement for postoperative hypothyroidism. However, serial calcium results at 3, 6, 12, and 20 months were within normal limits.

Thirty-two months after surgery, the patient presented emergently with new onset paresthesia, muscle cramps, fatigue, and syncope. Corrected serum calcium and parathyroid hormone measurements at this time were 5.0 mg/dL and 3.0 pg/mL (normal, 10–65 pg/mL), respectively. The patient was treated with calcium and vitamin D replacement, and the serum calcium level stabilized. The patient had no clinical evidence of disease on physical examination and fiberoptic laryngoscopy at the time of hypocalcemia. Subsequent imaging with CT and MRI revealed a 6.4 × 5.0 × 7.4 cm left-sided para-esophageal mass that demonstrated increased uptake on positron emission tomography. CT-guided biopsy of the mass revealed squamous cell carcinoma. The patient underwent attempted salvage concurrent chemoradiation therapy but subsequently died from uncontrolled disease.

**DISCUSSION**

Hypoparathyroidism after treatment for laryngeal and hypopharyngeal cancer has been previously described and may occur as a sequela of tumor invasion, surgery, radiation, and combined therapy.\(^4\)–\(^6\) Its occurrence following surgery alone, with reported incidences of 0 to 89%,\(^1\)\(^,\)\(^3\)–\(^7\) typically manifests within a few days after surgery and may be either transient or permanent. Multiple etiologies are associated with the occurrence of transient hypocalcemia, including temporary hypoparathyroidism, electrolyte abnormalities (hypomagnesemia), nutritional deficiencies (albumin, calcium, vitamin D), and intravascular fluid shifts (blood loss, transfusion, and replacement fluid). Permanent hypoparathyroidism, however, typically involves the excision or devascularization of a critical amount of parathyroid tissue. The extent of thyroidectomy incorporated with the resection is dependent on the location and extent of the lesion. Although hypoparathyroidism following a laryngectomy and total thyroidectomy is predictable, its occurrence after laryngectomy and ipsilateral hemithyroidectomy is more variable and is dependent on the degree of contralateral devascularization that occurs as a result of the neck dissection or mobilization of the preserved lobe.

The addition of radiation either preceding or following surgical therapy is associated with a higher degree of permanent hypoparathyroidism and is theorized to be a result of end vessel fibrosis.\(^1\)\(^,\)\(^4\) Thorp et al evaluated long-term thyroid and parathyroid function in a series of 28 patients with a least 5 years’ survival following therapy for laryngopharyngeal squamous cell carcinoma. The authors included both “partial” (normocalcemia with inappropriately low parathyroid hormone [PTH]) and “overt” (hypocalcemia with low PTH) as their study definition of hypoparathyroidism. Significant laboratory evidence of parathyroid dysfunction was noted in 88% treated with radiation alone, 67% treated with radiation followed by salvage laryngectomy, 89% treated with surgery and adjuvant radiotherapy, and 63% treated with
surgery alone. Although a subset of this group was noted to have hypocalcemia, the clinical correlation was not described. Additionally, the small numbers in each cohort and the inclusion of patients with “partial” hypoparathyroidism limits the generalization of the authors’ findings. Finally, since, the endocrine evaluation was performed 5 years following therapy without data at interval points, the natural history of the hypoparathyroidism is not described by this study.1 In contrast, Talmi et al detected no laboratory evidence of hypocalcemia 1 to 3 years after treatment in a report of 22 patients treated with multimodal therapy including irradiation for head and neck cancer. This series, however, represented a variety of head and neck pathologies, of which a subset was laryngeal cancer, and the extent of surgical resection was not described.3 Interestingly, multiple reports of elevation in parathyroid hormone levels with or without hypercalcemia have been reported after low-dose radiation to the neck for benign conditions and accidental exposure.8,9 This typically involves significantly lower doses of radiation than those used for treatment of head and neck malignancies.

The development of delayed hypoparathyroidism following therapy for laryngeal cancer has been previously described. Bromberg et al reported a patient who developed paresthesia and tetany secondary to hypocalcemia 2 years after pharyngolaryngectomy, neck dissection, and postoperative radiation therapy.7 However, serum calcium and parathyroid hormone levels in the interval between therapy and symptoms were not reported. Our case differs from prior reports of hypoparathyroidism after therapy for laryngeal cancer in multiple ways. The delay in endocrine dysfunction is documented by serial calcium measurements. The current patient had normal calcium values documented before and 1 year after concurrent chemoradiation therapy and over a 20-month period following salvage laryngectomy. Symptomatic hypocalcemia secondary to hypoparathyroidism subsequently developed 32 months after surgery. This represented the earliest sign of local recurrence that was not detected on either routine physical examination or fiberoptic laryngoscopy. The pathophysiology of delayed hypoparathyroidism in our patient is likely multifactorial, with extensive surgery, high-dose radiation therapy, and local recurrence acting as contributing factors. While the hemithyroidectomy performed as part of the laryngectomy would account for partial loss of parathyroid tissue, adequate initial endocrine function can be presumed from the long-term normocalcemia measured 20 months following therapy. As previously described, high-dose radiation therapy has also been linked to delayed endocrine dysfunction. Finally, local destruction of the remaining parathyroid tissue or local vasculature is presumed from the size, location, and timing of the recurrent tumor and may represent the dominant factor.

Our report in conjunction with reported rates of long-term parathyroid dysfunction suggest the role for lifelong surveillance for hypoparathyroidism in patients being treated for laryngeal cancer. While the early symptoms including paresthesias may be subtle, the occurrence of end-stage hypocalcemia may result in significant morbidity, including tetany, seizures, and arrhythmias. In addition to patient education regarding the early symptoms of hypocalcemia, routine testing of serum calcium and parathyroid hormone levels may be appropriate for high-risk patients. A rational algorithm for the surveillance of hypoparathyroidism in this population, however, requires further study. Prospective clinical and biochemical observation of a large cohort of patients treated for laryngeal cancer is required to identify the incidence, risk factors, and natural history of hypoparathyroidism following treatment for laryngeal cancer.

REFERENCES