

Short Communication

Head and neck non-metastatic cancer associated hypercalcemia

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ABSTRACT

Cancer associated hypercalcemia (CAH) is a relatively common paraneoplastic syndrome and may be associated with head and neck cancer patients. As the hypercalcemia may be life-threatening, recognition is paramount. Herein we investigate the prevalence and outcome metrics of CAH and create a proposed clinical guideline for advanced stage head and neck malignancies. We describe our experience with non-metastatic, asymptomatic persistent head and neck CAH, which resolved after surgical ablation. We have performed a literature search in the PubMed database between the years 1998-2018 using the key words "head neck", "squamous cell carcinoma", "hypercalcemia", "cancer associated hypercalcemia" and "paraneoplastic. Non-metastatic head and neck CAH generally presents in patients with advanced stage disease and is associated with poor prognosis (median survival time range 28-64 days). It may portend imminent distant spread. Most patients continue to suffer from persistent high calcium levels despite treatment. We present a patient with nodal recurrence of advanced stage IV oral cavity squamous cell carcinoma and CAH. Regional neck metastases were surgically excised, resulting in normalization of blood calcium levels. Hypercalcemia should be ruled out in all advanced head and neck cancers. Treating physicians should be aware and promptly treat severe hypercalcemia. CAH may herald advanced disease, thereby modifying treatment decisions. However, in cases where surgical ablation is feasible, it is the preferred management for achieving calcium normalization.

Keywords: Cancer associated hypercalcemia, Oral cavity carcinoma, Paraneoplastic syndrome, Head neck cancer

INTRODUCTION

Cancer associated hypercalcemia (CAH) without bone metastases may be diagnosed in a variety of solid tumors. It has been reported as the most frequent paraneoplastic metabolic condition.¹ Most reported cases had squamous cell carcinomas (SCC), with head and neck origin being the most frequent region for primary tumors.² CAH without bone metastases is usually found in patients with advanced disease.^{3,4} Exclusion of bone metastases is mandatory when serum phosphate is normal or slightly increased. Isotope bone scans are sensitive and may demonstrate bone metastases, but are also non-specific. Consequently, imaging with computer tomography or magnetic resonance imaging are preferred.⁵

The major player for CAH with no detectable bone metastases is high parathyroid hormone related protein (PTHrP), which is produced by tumor cells and cross reacts with the PTH receptor due to the similarity of the terminal peptides.⁵ Other factors, such as Tumor Growth Factor- α (TGF- α), Interleukin-1 (IL-1) and tumor necrosis factor (TNF), also have a role in CAH.¹

Like other solid tumors, hypercalcemia in head and neck cancers is more frequent in advanced disease and is associated with reduced survival.^{3,4,6} The clinical signs of hypercalcemia should be promptly recognized and treated. The clinical signs of cardiac abnormalities, nervous system depression, muscular weakness, gastrointestinal disturbance and renal failure, depend on the rate of development of the hypercalcemia.⁷ Anti-

hypercalcemic agents may temporarily improve functional and psychological status and reduce symptoms, but have little effect on the overall survival.⁷

Aims

- Investigating head and neck related non-bone metastatic CAH focusing on prevalence and prognosis outcome.
- Describe the treatment of hypercalcemia in this scenario, including our own experience with reversible hypercalcemia following tumor ablation.
- Establish a suggested clinical protocol for advanced head and neck cancer patients.

METHODS

Literature search of English language written papers between the years 1998 and 2018 using the PubMed database was conducted. The search words included "head neck", "squamous cell carcinoma", "hypercalcemia", "cancer associated hypercalcemia" and "paraneoplastic". All relevant studies were independently reviewed by two investigators.

An investigation of our experience treating an advanced head and neck, non-metastatic tumor with CAH reversed by surgical ablation is discussed. The patient has approved, by signing on a consent form, to discuss and publish an unidentifiable photograph.

RESULTS

Five studies (Table 1) investigating the occurrence and prognosis of head and neck CAH were published between the years 1998-2018.^{2,7-10} All except one analyzed CAH with and without bone metastases.⁷

Ramos et al studied 306 patients with solid tumors and CAH.² Twenty-eight percent of all study patients had head and neck tumors, which were the most common tumor site. Another study found that 5% of all head and neck malignancies had CAH. Lin and his group demonstrated a CAH annual incidence of 6.95% among head and neck patients.^{7,9}

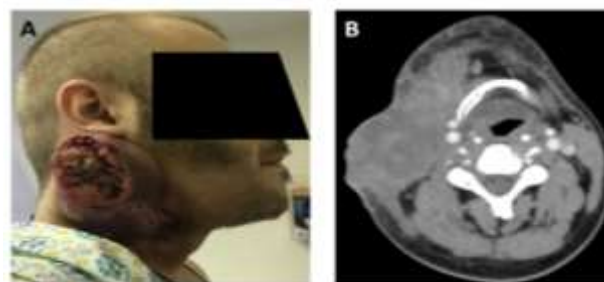


Figure 1: An advanced head and neck cancer associated hypercalcemia (CAH). Clinical (A) and Axial CT scan with radio contrast (B) demonstrating enlarged necrotic lymph node with aggressive extra nodal extension.

Table 1: Studies investigating head and neck non metastatic cancer associated hypercalcemia published between the years 1998 and 2018.

	Number of head and neck CAH patients	The proportion of head and neck patients out of all CAH	CAH Median survival time (days)	PTHrP elevation	Bone metastases (%)
Iwase et al ⁷	12	N.A.	54.9	+	0
Lin et al ⁹	91	N.A.	28	N.A	26
Le Tinier et al ⁸	186	84.5%	64	N.A	28
Penel et al ¹⁰	102	6.4-16% †	35	N.A	14.5
Ramos et al ²	85	28%	40	N.A	43

CAH: cancer associated hypercalcemia; PTHrP: PTH related protein; N.A: not applicable. † Site dependent (16% for oropharynx and oral cavity, 6.4% for laryngeal carcinoma)

Head and neck CAH, either by itself, or combined with leukocytosis, is negatively associated with survival.¹¹ A study by Iwase et al reviewed 242 patients with oral cavity SCC, of which 12 had both elevated serum calcium and PTHrP levels.⁷ All 12 CAH cases had advanced disease. With treatment, the quality of life was improved significantly, but hypercalcemia soon relapsed and the median survival was 53.5 days. Le Tinier and his group demonstrated other independent prognostic factors that further shortened overall survival; brain metastases, lymphocyte count $>1000/\text{mm}^3$, hypoalbuminemia and anemia.⁸ The median survival time in the study was 62 days. A study group of 102 head and neck patients with tumors originating in the oropharynx and oral cavity

(58%), hypopharynx (9.5%), and larynx (7.3%), altogether with esophagus and lung carcinomas, demonstrated a median survival time of 35 days among CAH patients.¹⁰ Factors associated with poor survival were male gender, presence of distant metastases, elevated alkaline phosphatase levels and hospitalization for intravenous hydration. A similar median survival time of 28 days was demonstrated by Lin et al.⁹ Reduced serum albumin, leukocytosis, clodronate use and short time interval to recurrent CAH with medical treatment had a statistically significant negative effect on survival.

Our group treated a non-metastatic advanced head and neck cancer patient with associated severe (although non-

symptomatic) CAH. The 31-years-old male patient underwent partial glossectomy followed by elective radiation therapy of the neck (in another institution) for a T2N0M0 oral tongue SCC. He presented to our clinic with palpable ipsilateral neck recurrence with skin involvement (Figure 1). PET-CT demonstrated massive necrotic regional lymphatic spread with neither bone nor lung metastases. The patient was scheduled for neck dissection and reconstruction for his advanced nodal disease (N3). Surprisingly, routine blood biochemistry investigation demonstrated severe (asymptomatic) life-threatening hypercalcemia, as high as 3.5 mmol/l (14 mg/dl), with normal albumin of 42 gr/l and a suppressed PTH level of 0.39 pmol/l. The patient had immediate intravenous fluids and aggressive diuresis treatment, which partially improved the calcium levels. However, a calcium level of 2.33 mmol/l (normal) was achieved only one day following a radical neck dissection, parotidectomy and myocutaneous flap reconstruction, with no need for further fluid and/or diuresis treatment. Three days later the patient was discharged with complete resolution of the hypercalcemia. Lung metastases subsequently developed and the patient died of the disease 8 months later with no recurrence of the CAH.

DISCUSSION

In this manuscript, we discuss the prevalence, prognosis and treatment of non-metastatic head and neck cancer associated hypercalcemia (CAH). We describe our experience of a dramatic reversal of the CAH following tumor ablation. Based on the literature review and on our own experience, we present a suggested clinical guideline for advanced head and neck cancers.

Head and neck CAH prevalence

Hypercalcemia is one of the most common life-threatening metabolic disorders in cancer. CAH develops in 10-20% of advanced solid tumors and is particularly frequent in head and neck SCC.¹²⁻¹⁵ Yet, the head and neck CAH rates vary in the medical literature as each group employed different statistical parameters; incidence, prevalence, and relative proportions of all solid tumors with CAH. Moreover, institutional differences affect study group patient selection (Table 1). Furthermore, most of the study groups in the last two decades did not exclude bony metastases and therefore cannot implicate a paraneoplastic phenomenon.^{2,8-10}

Head and neck CAH Prognosis

CAH negatively affects survival metrics (median survival time range 28-64 days). However, since bone metastases were not excluded, we may assume a bias affecting survival analysis of a group that may have consisted both metastatic and non-metastatic patients. Hypercalcaemia and leukocytosis are signs of advanced disease and of poor prognosis.^{11,15} Tumor-secreted TNF- α may be responsible for both leukocytosis and CAH. CAH may be

the first indication of a metastatic disease, which of course, could modify treatment decisions.

Head and neck CAH Treatment

Since CAH is generally slowly progressive, it allows for patient adjustment and most will be asymptomatic. If treatment is required, CAH may be persistent regardless of different treatment modalities. Hypercalcemic nephrogenic diabetes insipidus is treated by restoring the glomerular filtration rate with 0.9% saline infusions.¹⁶ Aggressive diuresis, together with calcitonin and bisphosphonates, is recommended. Bisphosphonates are responsible for osteoclast bone resorption inhibition, while calcitonin alters distal nephron calcium reabsorption.¹⁶ Iwase et al described blood calcium and PTH-rP levels reduction with calcitonin and bisphosphonates.⁷ This regimen was accompanied by improvement in six quality of life subscales (emotional functioning, cognitive functioning, fatigue, dyspnea, nausea/vomiting and appetite loss). However, the CAH inevitably recurred.

Similar to our experience, there is only one report of CAH resolution by excision of a supraglottic cancer (tumor stage was not provided).¹⁷ Tumor excision, when feasible, confers both oncologic benefit and appears to be an efficient and successful mode of therapy for CAH.

CONCLUSION

Physicians treating advanced head and neck cancers should be familiar with the entity of severe (sometimes asymptomatic) non-metastatic CAH. The routine biochemistry workup of advanced head and neck tumors should include calcium. If the levels are high, PTH / PTHrP blood levels should be ascertained. Unrecognized hypercalcemia is a potentially dangerous risk factor in patients requiring general anesthesia. CAH is a negative prognostic factor (stratification). Medical treatment consisting of fluid hydration, bisphosphonates and calcitonin, is unfortunately only temporarily successful. Surgical extirpation of the tumor mass causing the CAH seems to achieve a durable normalization of the calcium levels.

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