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CASE REPORT

Refractory Hypercalcemia in Squamous Cell Carcinoma of the Esophagus—a Case Report and Review of Literature

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Introduction

Hypercalcemia is a commonly encountered issue in malignancy, occurring in nearly 20 to 30% of patients at some point during their disease course [1]. Although malignancy, including squamous cell carcinomas (SCC), and primary hyperparathyroidism are most frequently associated with hypercalcemia other causes have also been identified [2]. Hypercalcemia of malignancy in solid tumors is a poor prognostic sign and nearly 50% of patients die within 30 days [3]. Lung and breast cancer are two of the most common causes of hypercalcemia in malignancy, but it has also been observed in esophageal cancer, with frequency of up to 21% [4].

Four mechanisms responsible for hypercalcemia of malignancy have been described. Humoral hypercalcemia of malignancy (HHM), the most common cause, involves secretion of parathyroid hormone-related protein (PTHrP). Other factors include osteolytic metastases mediated by osteoclasts with release of cytokines, 1,25-dihydroxyvitamin D (calcitriol) production from lymphomas and rarely, ectopic secretion of parathyroid hormone (PTH) [1]. In all these mechanisms, the resulting hypercalcemia suppresses PTH via negative feedback.

Previous cases of hypercalcemia in patients with SCC of the esophagus have been attributed to HHM with elevation of PTHrP and low to no detectable levels of PTH [4–6]. However, we present a patient with metastatic SCC of the esophagus with hypercalcemia but with elevated serum levels of both PTH and PTHrP. This appears to be the first case of SCC of the esophagus with an increase in both PTH and PTHrP.

Case Report

A 62-year-old male patient presented with a serum calcium of 16.7 mg/dL (reference range [ref] 8.4–10.3 mg/dL). He had been diagnosed with metastatic SCC of the esophagus with positron emission tomography-computed tomography (PET-CT) evidence of mediastinal lung, bone, and liver metastasis (Fig. 1). He had initially undergone an esophagogastroduodenoscopy (EGD) with biopsy of the lesion and balloon dilatation for dysphagia to solids. Immunohistochemical studies were positive for CAM5.2, p63, and focal CK5/6 but negative for CK7, TTF-1, CD56, synaptophysin, chromogranin, and PTH that was consistent with SCC (Figs. 2 and 3). He received chemotherapy with fluorouracil and carboplatin as well as radiation therapy for C1 and T2 metastasis. Despite this management, repeat PET-CT 3 months after his initial scan was significant for new cervical, hilar, and mediastinal lymphadenopathy along with hypermetabolic lesions in the proximal esophagus and vertebral bodies (Fig. 4). On routine blood work, he was found to have elevated calcium levels of 16.7 mg/dL leading to his hospitalization.

His initial presenting symptoms were nausea, constipation, and blurred vision, and he was started on volume expansion therapy with isotonic saline boluses followed by continuous normal saline infusion. He also received a dose of intravenous (IV) pamidronate and calcitonin on the second day of admission due to persistently elevated serum calcium levels (Fig. 5). IV furosemide was administered as he developed fluid overload leading to anasarca and he received another dose of IV pamidronate on day 7 of his admission. Despite this aggressive therapy, there was no significant improvement in serum calcium levels; therefore, cinacalcet therapy was initiated.

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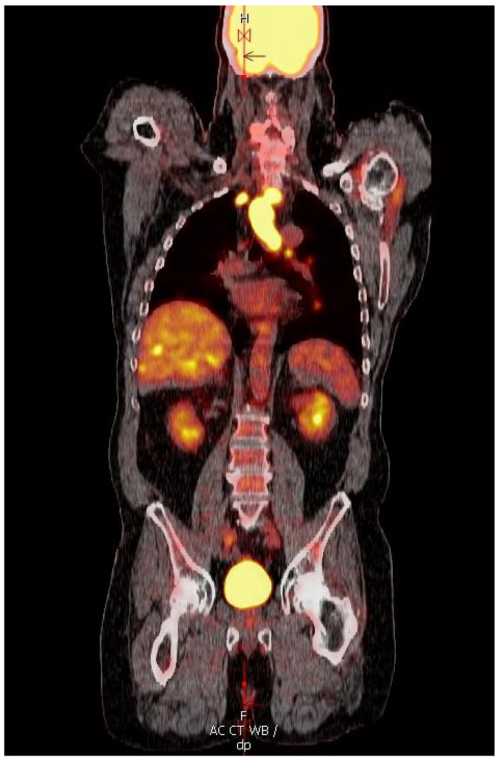

Fig. 1 Initial PET scan reveals intensely FDG avid upper to mid thoracic esophageal mass along with multiple hepatic and osseous metastases as well as left lower lobe nodules

Serum intact PTH on day 8 of his admission was 575.4 pg/mL (ref 11.0–68.0 pg/mL), which increased to 591.1 pg/mL on day 9 and 746.5 pg/mL on day 10. N-terminal PTHrP levels obtained on day 8 were elevated at 39 pmol/L (ref < 2.0 pmol/L). Parathyroid scintigraphy revealed normal uptake in the parathyroid gland, with expected washout on delayed images. There was no evidence of focal differential washout to suggest parathyroid adenoma. Throughout his hospital course,

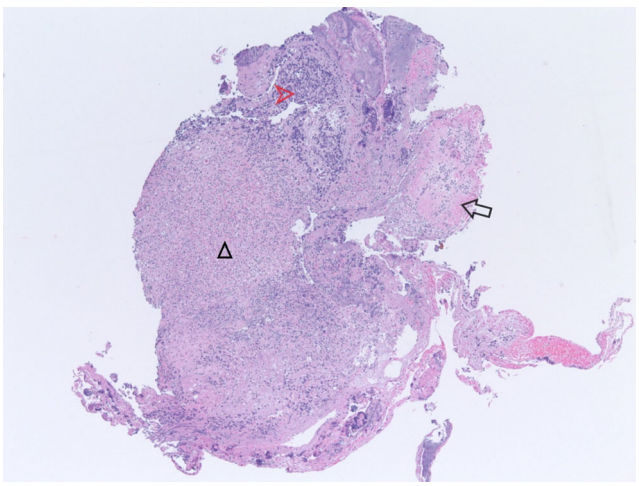

Fig. 2 Hematoxylin and eosin stain shows areas of necrosis (arrow), granulation (arrowhead), and poorly differentiated carcinoma (pointed arrow) on low-power field (× 40)

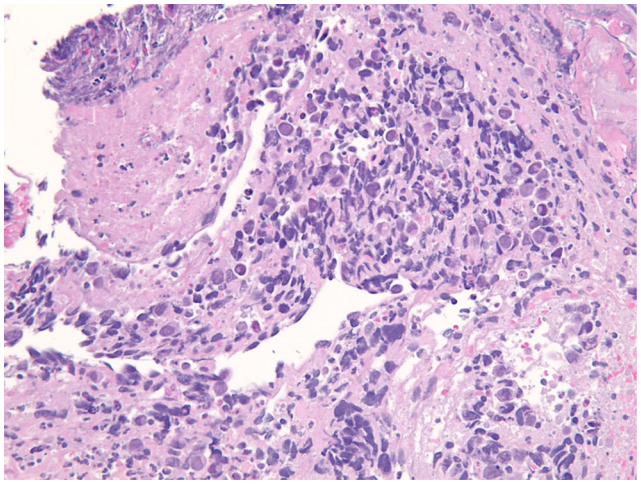

Fig. 3 High-power field (× 200) hematoxylin and eosin stain shows poorly differentiated, hyperchromatic, pleomorphic, epithelioid pattern with high nucleus-to-cytoplasm ratio

serum creatinine and glomerular filtration rate (GFR) remained normal. 25-hydroxyvitamin D levels were slightly low 28.6 ng/mL (ref 30.0–100.0 ng/mL), whereas 1,25-dihydroxyvitamin D was 70 pg/mL (ref 19.9–79.3 pg/mL).

His hospital stay was complicated by worsening of his mental status. Unfortunately, his calcium levels continued to rise (Fig. 5). He was offered the option of emergent hemodialysis for refractory hypercalcemia, but the patient and his family decided to pursue comfort measures. The patient died on day 12 of admission.

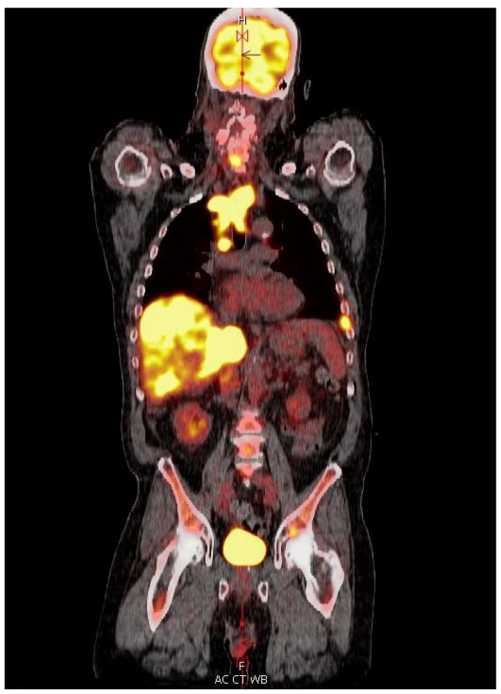

Fig. 4 PET scan after 3 months shows progression of disease with hypermetabolic lesion in the esophagus, new lymphadenopathy, and interval increase in diffuse bony and hepatic metastatic disease

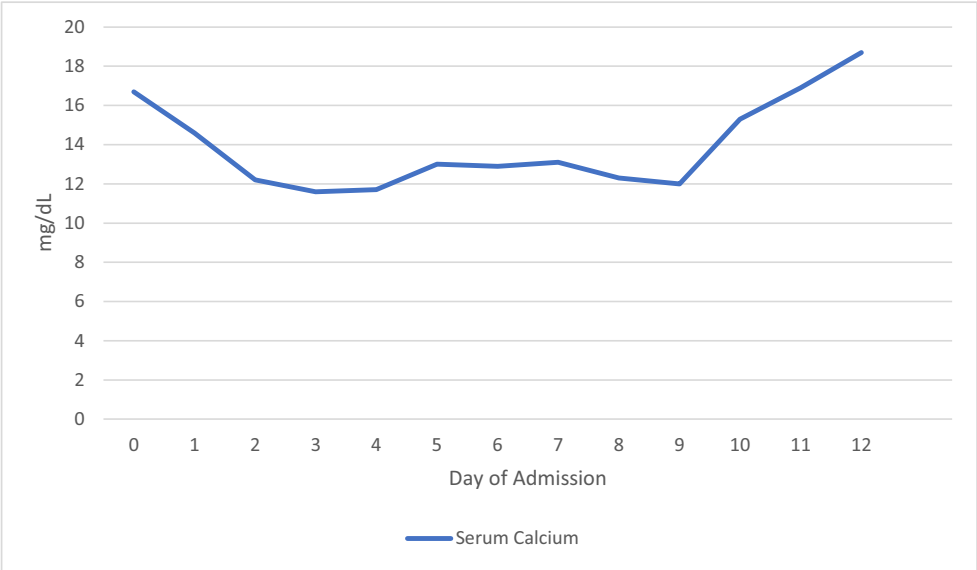

Fig. 5 Serum calcium levels during the patient's hospital stay (reference range 8.4–10.3 mg/dL)

Discussion

As previously mentioned, four different mechanisms for hypercalcemia of malignancy including HHM, local osteolytic hypercalcemia, calcitriol-secreting lymphomas, or ectopic PTH production have been described. HHM is most often associated with solid malignancies, including both SCC and adenocarcinomas [7], resulting in suppression of PTH release due to negative feedback from hypercalcemia.

Prior studies have shown hypercalcemia with SCC of the esophagus. An extensive review involving 170 patients with esophageal cancer was performed at the Department of Veteran Affairs. It was found that 47 patients (27.6%) had increased calcium levels and all but one had SCC. However, this study did not report the values of PTH or PTHrP [8]. Similarly, a study in Japan evaluated the incidence of hypercalcemia in esophageal cancers. Of the 360 patients with SCC of the esophagus, 47 (13.1%) were found to have hypercalcemia. PTHrP was evaluated in 11 hypercalcemic patients and was elevated in all of them, while serum PTH was only checked in 16 patients, none of whom had increased levels [9].

Most of the patients previously described with SCC of the esophagus with hypercalcemia have been reported with low PTH [4–6]. However, in one study, elevated PTH were discovered in two patients with SCC of the esophagus, but PTHrP levels were not evaluated [10].

Hutchesson et al. assessed 47 patients with hypercalcemia. Of the seven patients with elevated PTH levels, only one patient with myeloma and bronchial carcinoma also had elevated PTHrP levels (3.0 pmol/L) and survived only 9 days after development of hypercalcemia [11]. There also has been a single report of a patient with neuroectodermal tumor with elevation of both PTH and PTHrP [12]. Similarly, in a Chinese study on hypercalcemia, seven patients with coexisting malignancy and primary hyperparathyroidism were identified, all with elevated PTH. PTHrP was elevated in three patients, but none of them had SCC of the esophagus [13].

PTHrP is a useful marker to predict response to therapy in patient with hypercalcemia. One study found that PTHrP of 12 pmol/L or more was associated with poor response to pamidronate therapy [14]. Recurrence of hypercalcemia within 14 days of therapy may also occur with elevated PTHrP levels.

Although elevation of both PTH and PTHrP have been reported in the past, no previous report has revealed elevation of both these markers with SCC of the esophagus. In our patient, serum creatinine and GFR remained normal throughout his hospital course, whereas vitamin D levels were only mildly low, indicating against secondary hyperparathyroidism as a likely cause of PTH elevation. Negative parathyroid scintigraphy also ruled out parathyroid adenoma as another potential etiology. This indicates that there may be ectopic production of PTH but at the same time, elevated PTHrP also reveals HHM. However, immunohistochemical (IHC) stain for PTH was also negative, suggesting ectopic PTH production from another site. No other case report has described presence of both these mechanisms in the same patient with SCC of the esophagus and hypercalcemia. Our case highlights the need to check both PTH and PTHrP levels in patients with hypercalcemia of malignancy for more accurate diagnosis, which has also been previously suggested [13].

Author Contributions H. Arif, M. Beg and S. Zahid reviewed the literature and drafted the manuscript. M. Sial and A. Christou were involved in the care of the patient and edited the manuscript. A. Talwar provided and described pathology reports. M. Babich edited the final manuscript. H. Arif is the article guarantor.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was verbally obtained for this case report.

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