CASE REPORT

Complete resolution of refractory hypercalcemia following pneumonectomy in squamous cell carcinoma of the lung

Doraid Alrifai1*, Styliani Germanou1, Brendan Tinwell1, Edward Cetti2, Ian Hunt1, Tim Benepal1

1 St George’s University Hospitals NHS Foundation Trust, London, United Kingdom
2 Surrey and Sussex Healthcare NHS Trust, East Surrey Hospital, Redhill, Surrey, United Kingdom

Abstract: Patients with squamous cell carcinoma of the lung, amenable to complete resection, can suffer symptomatic humoral hypercalcemia of malignancy (HHM). This can compromise performance status and, ultimately, the candidacy for resection. Two cases highlighting initial pharmacological attempts at pre-operative correction of both clinical performance and elevated serum calcium levels are reported. Both patients received unsuccessful treatment leading to premature cessation of pharmacological measures and ultimately proceeded to complete tumor resection.

Keywords: squamous cell carcinoma; lung cancer; HHM; humoral hypercalcemia of malignancy

Case report

The first case involved a 68-year-old Caucasian male with a 40-pack/year tobacco history, who presented with recurrent chest infections. Following a computerized tomography (CT) scan of the thorax, abdomen and pelvis, a lesion at the upper left lobe of the lung was identified, consistent with lung carcinoma. A biopsy of this lesion confirmed squamous cell carcinoma (Figure 1). A positron emission tomography (PET)-CT scan revealed a large left upper lobe mass. The clinical stage was confirmed as T3N0M0.

The diagnosis was complicated by symptomatic refractory hypercalcemia, resulting in an Eastern Cooperative Oncology Group (ECOG) performance status of 3. Following clinical assessment, the patient was deemed an unsuitable surgical candidate, and therefore initial disease management focused on improving his general physical condition prior to general anesthesia.
Figure 1. Poorly differentiated, focally keratinizing squamous cell carcinoma exhibiting strong nuclear immunoreactivity for p63 [hematoxylin and eosin (H&E) and immunostained section at ×100]

patient’s serum parathyroid hormone-related protein (PTHrP) levels were unknown. The patient was unsuccessfully treated with bisphosphonates including ibandronic acid and zolendronic acid, followed by denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL). As his condition and corrected calcium did not improve, chemotherapy was then delivered, given the likelihood of this being paraneoplastic in nature.

Both vinorelbine and cisplatin were administered with no improvements in the hypercalcemia. Given the lack of clinical and biochemical response to pre-operative treatment and the risk of disease progression, the patient underwent an uncomplicated left pneumonectomy and lymph node dissection. The pathological specimen was confirmed to be a completely resected, extensively necrotic, 100-mm, poorly differentiated squamous cell carcinoma. Immunohistochemistry supported the morphological diagnosis evidenced by tumor cells staining positive for p63 and CK5, and negative for TTF-1. Visceral pleural and vascular invasion was present. Metastatic carcinoma was also present in a station 6 and intrapulmonary lymph node. There were no features to suggest extracapsular nodal spread. The final pathological staging was pT3 pN2. Almost immediately following resection, the corrected calcium levels returned to within normal limits, and the patient’s performance status returned to zero (Figure 2). No further chemotherapy was delivered following surgery.

The second case involved a 72-year-old, non-smoking male with a 6-month history of cough and weight loss. A right upper lobe lung lesion was confirmed to be poorly differentiated non-small cell carcinoma, favoring squamous cell carcinoma. PET-CT confirmed a clinical stage of T3N0M0 (Figure 3).

Similarly, the patient also developed symptomatic refractory hypercalcemia resulting in an ECOG performance status of 3. Protein electrophoresis, Bence-Jones protein levels, a serum immunoglobulin panel, calcitonin, prostate-specific antigen (PSA), angiotensin converting

Figure 2. Serum-corrected calcium level against time. An established resolution following pneumonectomy

Figure 3. Chest X-ray representing the right upper lobe tumor
enzyme (ACE) and vitamin D were all unhelpful in identifying the cause. Serum PTHrP was not requested for this case either.

Serum-corrected calcium levels did not respond to zolendronic acid, ibandronic acid or denosumab.Gemcitabine and carboplatin chemotherapy was delivered with no success, followed by paclitaxel on a weekly schedule. Despite these attempts, the hypercalcemia remained refractory and the patient’s performance status remained problematic. Surgery was suggested following unsuccessful attempts at pharmacologically controlling the elevated calcium levels and improving the patient’s physical state. A pneumonectomy and lymph node dissection was performed. This confirmed a 70-mm, poorly differentiated, squamous cell carcinoma with no vascular invasion. The sampled hilar and mediastinal lymph nodes were negative for metastatic carcinoma. The final pathological stage for this specimen was pT2b pN0. The patient recovered well with complete resolution of symptoms and corrected calcium levels (Figure 4). The patient did not receive adjuvant chemotherapy as he received chemotherapy preoperatively. He continues to do well. There have been no signs of relapsed disease, or hypercalcemia.

![Figure 4. Serum calcium levels against time: demonstrating non-sustained resolution of hypercalcemia until pneumonectomy](image)

**Discussion**

HHM can be found in as high as 30% of patients with malignancy. The most common tumors include lung cancer, breast cancer and multiple myeloma. Frequent causes of hypercalcemia in malignancy include bone metastases, elevated PTHrP levels, elevated parathyroid hormone (PTH), high 1-25(OH)2 vitamin D3 and 1α-hydroxylase levels[2]. PTHrP was thought to be a common mediator of HHM, and studies have suggested that almost 90% of solid tumors have detectable PTHrP in the presence of HHM[3]. Moreover, it has been suggested that squamous cell carcinoma accounts for between 40%–50% of HHM cases, the majority of which were diagnosed at an advanced stage[4,5].

Pre-clinical studies have identified PTHrP antigen in 100% of squamous cell carcinoma specimens (34 out of 34 cases). Other tissue specimens assessed included breast cancer (1/6), adenocarcinoma (0/15), renal (4/4), melanoma (2/2) and small cell carcinoma (3/3). Results of these high levels of expression in squamous cell carcinoma have been supported by other studies[6].

The use of surgery to treat HHM has been rarely documented in the literature. Animal models with human oral cavity and lung cancer developed HHM, which resolved rapidly following resection of these primary tumors[7]. Complete resection of pulmonary squamous cell carcinoma in humans has been reported in the setting of HHM. These cases have resulted in resolved refractory hypercalcemia[8,9].

In both reported cases, the performance status of each patient dictated management and precluded initial surgical treatment. This led to attempted pharmacological control of serum calcium levels and symptoms to optimize the patient’s condition prior to complete resection. Both cases were treated with the intention to cure. Furthermore, cases of cytoreductive tumor resections to control HHM have not been reported to our knowledge.

Moreover, both cases did not proceed to adjuvant chemotherapy, given that each patient received chemotherapy prior to resection. Modest improvements in overall survival have been observed in patients receiving adjuvant chemotherapy; however, these patients never received pre-operative chemotherapy, therefore it is not directly comparable[10]. Post-operative radiotherapy is not routinely used for completely resected early stage lung cancer (I + II), although patients with N2 disease can be considered for it[11].

Resolution of HHM by removing the primary tumor suggests that it is the driving factor. Pre- and post-operative serum PTHrP were not measured in the case studies but it may play a role in demonstrating a relationship between tumor resection and HHM resolution. We have shown that although we have proficient drugs to tackle hypercalcemia, the optimal management in this setting is complete resection. Although a credible approach, drug administration may lead to delays in definitive treatment and ultimately increase the risk of progression of the malignancy. These symptomatic patients
can be considered for curative surgery followed by adjuvant chemotherapy, if appropriate.

The above cases represent patients with squamous cell carcinoma of the lung and symptomatic refractory hypercalcemia, which responded both clinically and biochemically to resection of the primary tumor. Surgical resection of these tumors can be considered upfront; however, the impact on performance status can pose a significant risk when considering general anesthesia and major thoracic surgery. Careful surgical planning is required if this is to be considered. Systemic treatment in this context may lead to delays in surgery and increase the likelihood of metastases. Earlier surgical input in these unique patients can be considered in order to assess suitability for resection and further treatments to control this metabolic abnormality prior to surgery.

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Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References