Small cell carcinoma lung presenting as life-threatening hypercalcemia - A rare association

Sir,

Hypercalcemia is a commonly reported metabolic complication in various malignancies. The most common cancers associated with hypercalcemia include non-small cell lung cancer, breast cancer and multiple myeloma.\(^1\) Hypercalcemia is usually associated with advanced malignancy and is a poor prognostic sign.\(^1\) Hypercalcemia is a very unusual complication of small cell lung cancer (SCLC) even in the presence of bone metastases. The molecular mechanisms that mediate hypercalcemia in SCLC are not yet fully understood.

We present here the case of a 50-year-old male, previously healthy, heavy current smoker who presented with 2-3 days of recurrent vomiting followed by generalized tonic clonic seizures and altered sensorium since 1 day. On presentation to the emergency room, he was grossly dehydrated and hypotensive with a blood pressure of 70 systolic mmHg. There were no signs of raised intracranial tension or meningeal irritation. He was resuscitated with intravenous fluids and a non-contrast CT scan of the head performed in the emergency was normal. Further investigations revealed a hemoglobin of 14mg/dl, TLC 13,900 cumm with neutrophils of...
90%. Blood urea was 200 mg/dl and creatinine was 1.9 mg/dl. Serum sodium was 132 mEq/L and serum potassium was 5.2 mEq/L. Total serum calcium levels were markedly elevated at 16.4 mg/dl. EKG done in the ER was suggestive of sinus tachycardia with heart rate of 140/minute with ST-T changes in all precordial leads, with shortened QTc interval. The patient was resuscitated with intravenous fluids along with fruseamide and 4 mg of IV Zolendronic acid. The patient was admitted to the ICU and over the next 48 hours the general condition of the patient gradually improved.

To evaluate the cause of hypercalcemia, recommended blood biochemistry was done, which revealed normal phosphorus levels - 4.3 mg/dl, alkaline phosphatase - 118 IU/L (normal). Serum parathormone (PTH) levels were 4.8 pg/ml (increased); parathormone-related peptide (PTHrP), which is implicated in many cases of malignancy related hypercalcemia, was <1 (negative). Serum 1.25 (OH) vitamin D and 25-OH vitamin D were normal. Thyroid profile and serum protein and albumin levels were normal.

A routine chest X-ray was done which revealed right para-hilar prominence. A contrast-enhanced CT (CECT) chest was done subsequently, which revealed a right hilar mass lesion and multiple enlarged mediastinal lymph nodes [Figure 1].

To evaluate further, the patient underwent fiberoptic bronchoscopy (FOB), with endoscopic bronchial ultrasound (EBUS)-guided fine needle aspiration (EBUS-FNA) of the mediastinal lymph nodes. Mucosal infiltration and luminal narrowing was noted in the right main bronchus and the right upper lobe bronchus. Endobronchial biopsy (EBB) was taken from the mucosal infiltration.

EBUS cytology and cell block showed extensive crush artifact with small round cells, suggestive of small cell carcinoma lung. EBB showed metaplastic bronchial epithelium, and subepithelium showed infiltration by small round cells with hyperchromatic nuclei and extensive crush artifact. These findings were suggestive of small cell carcinoma lung and the final diagnosis was confirmed by immunohistochemistry (IHC), which revealed that the tumor tissue was CD56 and synaptophysin positive. Neuron-specific enolase (NSE) was focally positive [Figure 2]. Chromogranin was negative. CK 7 and TTF 1 were negative.

For further metastatic work up, a positron emission test (PET) scan was done which revealed a hypermetabolic 6.8 x 5-cm mass lesion involving the right hilar and infranilar region encasing the right upper lobe bronchus and bronchus intermedius with multiple FDG avid mediastinal lymph nodes. The tumor had metastasized to the adrenals and there were multiple lytic lesions in the calvarium, cervico-dorsal-lumbar vertebrae, scapulae, humerus, clavicles, sacrum, and femur [Figure 3].

As the general condition of the patient improved, he was started on chemotherapy with cisplatin and etoposide. This was followed by prophylactic cranial irradiation and monthly IV bisphosphonates (zolendronic acid). The patient has completed three cycles of chemotherapy and serum calcium levels are maintained in range now.

Hypercalcemia is a very rare and unusual metabolic complication in SCLC patients. The exact molecular mechanism of hypercalcemia in SCLC is not known. Hypercalcemia in patients with osteolytic metastases is primarily due to increased bone resorption and release...
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of calcium from bone, whereas hypercalcemia in patients with tumors secreting PTHrP is due to both increased bone resorption and distal renal tubular calcium reabsorption. In patients with tumoral production of 1,25-dihydroxyvitamin D, hypercalcemia is the result of a combination of increased bone resorption and intestinal calcium absorption. Although multiple bony metastasis may lead to systemic hypercalcemia, more than one mechanism have been implicated. Also, it has been noted that while bone metastases are common in SCLC its association with hypercalcemia is not constant. There are isolated case reports of PTHrP-mediated and PTH associated hypercalcemia in patients with SCLC.[3] Most patients with hypercalcemia and SCLC seem to have bone or bone marrow involvement.[3] It is therefore, speculated that bone marrow involvement by SCLC may lead to cytokine production with subsequent osteoclastic stimulation, leading to hypercalcemia. The plausible mediators may include RANK-L, TNF and IL-6.

The treatment of hypercalcemia in these patients includes IV hydration with loop diuretics along with treatment of life-threatening arrhythmias, followed by bisphosphonates and calcitonin.[4] Denosumab is recommended in patients with refractory hypercalcemia or in patients with renal dysfunction, where bisphosphonates are contraindicated.[5] Dialysis is generally reserved for those with severe refractory hypercalcemia not responding to conventional medical therapy.

Our patient had hypercalcemia with normal serum phosphorus level thus, ruling out primary hyperparathyroidism as a cause of hypercalcemia. His serum PTH level was suppressed and circulating PTHrP was absent. Other common causes of hypercalcemia were ruled out. He did not have raised vitamin D levels, associated plasma cell dyscrasias, thyroid abnormalities or any other underlying granulomatous disease.

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Pathogenesis of bilateral chylothorax after injury of thoracic duct during central venous catheterization

Sir,

I read with interest the article by Saxena et al.[1] and would like to raise the following issues:

1. The authors have described a case of bilateral chylothorax following left‑sided central venous catheterization but have not elucidated the pathophysiological mechanism of bilateral chylothorax due to injury to the thoracic duct (which lies on the left side).

It is known that injury to the thoracic duct below T5 results in right‑sided chylothorax, between T3 and T5 to bilateral chylothorax and injury above T3 leads to left‑sided chylothorax (as can be seen from Figure 1). However, in the case described by the authors, bilateral chylothorax resulted from a direct injury to the thoracic duct probably during left internal jugular vein (IJV) cannulation. How can that be explained? Contemporary literature also does not elaborate on to the reason for the same. However, it appears based on reports of injury to lymphatic ducts (albeit in different scenarios such as thoracic duct ligation) that accumulation of chyle bilaterally due to unilateral injury to the thoracic duct may be due to the following reasons: