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Malignant Hypercalcemia from an Unspecified Lung Cancer

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Abstract **Case Report**

Patients with active neoplasms may be prone to collateral complications from tumor burden. Different mechanisms of action have been postulated in the medical literature regarding endocrinologic activity and paraneoplastic processes from neoplasms. Particularly, electrolyte imbalances such as hypercalcemia can become a medical emergency on some of these patients since it has the potential to affect multiple organ systems. We present a case report of a patient who developed altered cognition, pulmonary and renal impairment due to hypercalcemia of malignancy from an unspecified lung neoplasm.

Keywords: Hypercalcemia, cancer, parathyroid hormone related peptide.

INTRODUCTION

Hypercalcemia of malignancy has been attributed to different neoplastic entities including multiple myeloma, renal cell cancer, breast cancer and lung cancer [1]. Clinical presentation may vary from patients being asymptomatic to severe multi-organ impairment including renal failure, abdominal pain, constipation, cardiac arrythmias, obtundation, coma or death. Symptoms are not readily apparent but if present, they usually carry a poor prognosis. Current treatment options depend on the serum calcium and symptomatology. Mild hypercalcemia is usually defined as serum Ca<12mg/dL, moderate hypercalcemia 12-14mg/dL and severe hypercalcemia as >14mg/dL [2]. While mild hypercalcemia may be asymptomatic or require no treatment, moderate and severe hypercalcemia should always be identified and promptly managed. Pharmacologic treatment focuses on the mechanisms affecting bone and calcium metabolism with a target goal of normalizing calcium serum levels with the end-goal of ameliorating end-organ burden. Options include aggressive hydration, diuretic medications, calcitonin and in the case of underlying neoplasms, bisphosphonate therapy [3]. We present a case of a 67-year-old female who presented with a severe hypercalcemia of 17.5mg/dL with radiologic imaging suggesting an underlying lung cancer.

CASE REPORT

Patient is a 67-year-old Female with a past medical history of diabetes mellitus type 2, hypertension, stroke with residual right-sided weakness and chronic obstructive pulmonary disease who presented to the Emergency Department complaining of progressively worsening shortness of breath and productive cough for 7 days. She was seen by her primary care physician outpatient, who prescribed 2 courses of Azithromycin then one course of Levofloxacin without improvement of symptoms. In addition, she presented with generalized weakness, fatigue, decreased appetite, and emotional irritation. Initial vital exam revealed blood pressure of 112/51mmHg, temperature of 97.7F, tachycardia of 104 beats per minute, respiratory rate of 18 breath/minute and oxygen saturation of 95%. Physical exam was remarkable for patient being irritated, ill-appearing, pressure speech, mucous membranes dry, decreased breath sounds on the lower lobe of the right lung and tachycardia with regular rhythm. Physical exam was limited as patient became agitated and requested not to be further examined. Initial bloodwork revealed a

leukocytosis of 12,200, thrombocytosis of 397,000, hyponatremia of 131, hypokalemia of 3.2, metabolic alkalosis of 39, random glucose of 126, hypercalcemia of 17.5 and hypomagnesemia of 1.4. An electrocardiogram revealed normal sinus rhythm at a rate of 94beats per minute, QTc interval of 405ms, left axis deviation and an inferior infarct of undetermined age. A chest X-ray revealed a 1.7cm round nodule in the right lower lobe and large airspace disease in the left lower lobe. A head computer tomography revealed no acute intracranial abnormality, except for moderate age advanced global parenchymal volume loss. A chest computer tomography revealed a 10cm soft tissue mass at the central portion of the upper lobe of the left lung which cannot be separated from the left appendage of the left atrium, multiple small masses and nodules in both lungs suggestive of metastatic process and a large soft tissue mass lesion in the left adrenal gland consistent with metastasis. Our patient received 1000 mL of normal saline, 1gm of Ceftriaxone, 40mg of Furosemide, 20meQ of potassium chloride and she was admitted to telemetry for further evaluation. Pulmonology, nephrology, and Hematology/Oncology services were consulted. During hospital day #0, her home medications Metformin 1000mg BID and Lisinopril 10mg daily were restarted. In addition, our patient was initiated on nebulizer treatments with Albuterol/Ipratropium, Budesonide every 6 hours as needed, Methylprednisolone 40mg IV every 12 hours, Doxycycline 100mg IV every 12 hours, continuous 0.45% normal saline at a rate of 40cc/hr. On hospital day #1, patient's serum calcium decreased to 16.0. A serum parathyroid hormone level was low at 5pg/mL, serum parathyroid hormone related protein (PTHrp) was elevated at 83pg/mL and a 25-hydroxy Vitamin D level was normal at 30ng/mL. Patient was given a one-time dose 3.5mg of Zoledronic acid and started on 200 I/U of intranasal Calcitonin BID. Her maintenance fluids were changed to 0.9% normal saline and fluid rate was increased to 100cc/hr. Clinically, she remained irritated, refusing to answer questions, or being examined physically. Interventional radiology was consulted for tissue sampling biopsy; however, our patient initially refused the procedure. On hospital day #3, the serum calcium decreased to 13.7. Clinically, patient was more cooperative and agreed to undergo tissue biopsy of the lung lesion. Interventional radiology collected a lung tissue sample using a 19-gauge needle. Position was confirmed via CT imaging. Using a coaxial technique, multiple core biopsies were obtained from the left upper lobe anterior lung mass. Biopsy samples were sent to the pathology laboratory. Through her hospital course, our patient continued receiving Calcitonin 200 I/U intranasally twice a day and IV maintenance fluids. Her serum calcium decreased to 11.8, 10.0, 9.4 and 9.5, through the following days. A pathology report from lung tissue revealed predominantly necrotic tumor containing scant atypical cells, highly suspicious for malignancy; however, tumor classification was precluded given scant cellularity. A repeat lung biopsy was planned but patient refused further evaluations. She was discharged on hospital day #5 after her symptoms improved and all her serum electrolytes normalized. The patient returned to the Emergency Room 2 months later due to altered mentation. Palliative services were consulted, and she was placed in hospice care. Patient expired hours after being admitted.

DISCUSSION

Multiple organs are involved in calcium metabolism. One of the principal regulators include the parathyroid glands which secrete parathyroid hormone (PTH). When calcium is low, PTH binds to receptors in the renal tubules promoting calcium reabsorption. In addition, PTH increases osteoblastic maturation leading to increase osteoclastic activity, causing bone resorption of calcium into the bloodstream. PTH also promotes the activation of vitamin D to its active form, which in effect, promotes calcium reabsorption in the gastrointestinal tract [4]. The mechanism of increased serum calcium in patients with neoplastic processes varies depending on the type of tumor. In bone metastasis, there is increased cytokine activity such as Tumor Necrosis Factor and Interleukin-1, which promotes proliferation of osteoclasts, which in turn increase calcium resorption from bone [5]. In multiple myeloma, there is an increased secretion of osteoclast activating factors interleukin-6, RANK-ligand, lymphtoxin which produce a similar response [6]. Hypercalcemia can also be due to solid tumors and Non-Hodgkin lymphoma secreting parathyroid related peptide (PTHrp), which acts analogous to parathyroid hormone; however in an autonomous fashion [7].

The clinical presentation of malignant hypercalcemia depends on the magnitude of serum calcium levels and/or the acuity of rise in serum calcium, regardless of etiology. In general, patients with a modest increase in calcium (<12mg/dL) may present asymptomatic or with mild symptoms of depression and fatigue. When calcium levels rise >12mg/dL but <14mg/dL, patient may present with urinary symptoms, including polyuria, nocturia, polydipsia, dehydration as well as nausea, weakness, depression. Patients with severe hypercalcemia >14mg/dL) may present with severe weakness, stupor or even coma. Urinary symptoms are thought to be secondary to calcium acting as a diuretic agent as a physiologic conduit to eliminate excessive calcium. It does so by binding to calcium-sensing receptors in the basolateral membrane of the Loop of Henle and thick ascending loop in the nephron apparatus [9]; which in turn, inhibits sodium and calcium reabsorption, and ultimately increase water excretion. Gastrointestinal manifestations including constipation and abdominal pain are thought to be due to a dysregulation of smooth muscle function and dysautonomia [10]. Neurologic symptoms including irritability, depression, stupor and coma are thought to be due to extracellular changes in electrochemical

homeostasis, which is required for optimal neurologic functioning [8]. Our patient exhibited multi-organ failure from severe hypercalcemia which possibly derived from a neoplastic process, given CT scan findings and clinical presentation.

The treatment of hypercalcemia depends on laboratory values and clinical presentation. For patients with calcium levels exceeding 14mg/dL treatment focuses on decreased bone reabsorption, increased calcitonin; which in turn inhibits PTH and aggressive IV hydration [11] as patients present with varying degrees of polyuria and intravascular volume depletion. Our patient received Zoledronic acid 3.5mg, intranasal calcitonin twice a day and IV maintenance fluids which provided clinical and biochemical improvement.

CONCLUSION

Hypercalcemia of malignancy can pose an imminent thread to a patient's life. Current medical literature proposes multiple mechanisms accounting for this electrolyte derangement and treatment options depending on clinical presentation. Depending on the severity of calcium elevation, patient may present with different degrees of symptoms. Although, our tissue sampling from lung biopsy was not diagnostic, this patient's clinical history, laboratory findings and imaging results are most consistent with a lung neoplasm. Our case presentation aligns with the current medical literature and reinforces the need for aggressive IV hydration, anti-resorptive therapy and calcitonin use in severe hypercalcemia of malignancy.

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