ISSN: 2634 - 680X

Journal of Clinical Case Studies Reviews & Reports

SCIENTIFIC Research and Community

Case Report

Open Access

Hypercalcemia: An Ominous sign of Malignancy

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ABSTRACT

Hypercalcemia is a disorder commonly encountered by primary care physicians. The diagnosis often is made incidentally in asymptomatic patients Clinical manifestations affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems. 90% of cases of hypercalcemia are due to primary hyperparathyroidism and malignancy. This article highlights the importance of proper work-up of elevated serum calcium levels and complications that can arise from failure to do so. This is a case report of a 63-year-old female who was found to have asymptomatic hypercalcemia of 10.5 mg/dl but was lost to follow up and presented four years later to her primary care physician with complaints of pain in the neck and weakness in bilateral shoulders, arms, wrists, and numbness of 4th and 5th digits. MRI revealed lytic lesions on the cervical and thoracic spine with compression deformity likely due to metastatic breast cancer. Lab reports revealed a serum calcium level of 12.1mg/dl and the patient's chart (mammogram/ breast US) confirmed malignant breast cancer.

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Received: May 27, 2021; **Accepted:** June 07, 2021; **Published:** June 10, 2021

Keywords: Hypercalcemia, Malignancy, Hyperparathyroidism, Elderly

Background

Hypercalcemia secondary to malignancy is a common consequence for patients with cancer; approximately 10 to 30% of all patients with cancer will show hypercalcemia [1]. Hypercalcemia is most common in later-staged malignancies and thus shows a poorer prognosis [2]. The most common cancers showing an increase in calcium are breast, renal, lung, and multiple myeloma [2]. Other causes of hypercalcemia include overactive parathyroid glands, granulomatous diseases, immobility, dehydration, medications, and supplements [1,3]. It is therefore important to get a complete history including both prescribed and over-the-counter medications, especially thiazide diuretics, Lithium, vitamin D, and antacids containing calcium carbonate. However, hypercalcemia in a primary care setting is often overlooked.

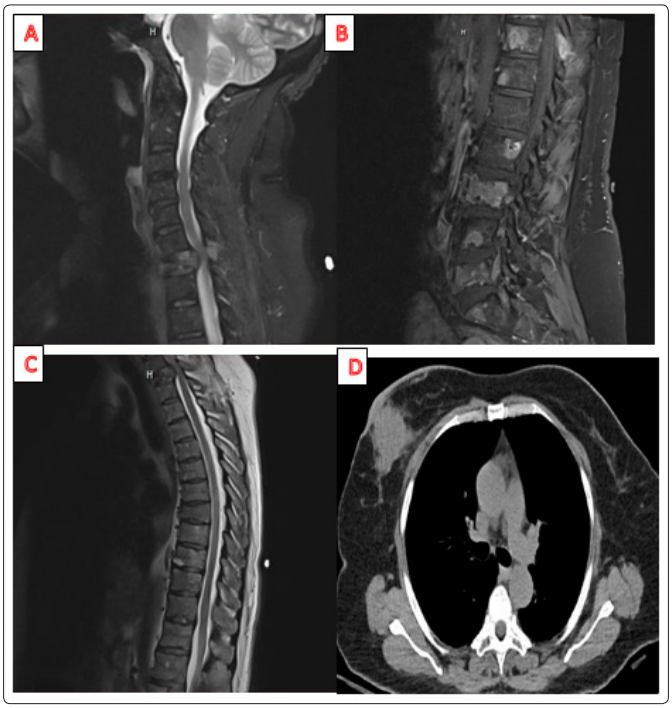
Case Summary

A 63-year-old African American female with a past medical history of hypertension presented to the primary care office for routine screening and evaluation. In 2020, the patient presented with complaints of worsening pain and weakness in bilateral shoulders, arms, wrists, and upper back for two months. She had numbness on the lateral aspect of her upper extremities with associated neck pain. She further reported difficulty grasping objects which often led her to lose control and drop the object. At that time, the patient was given supportive care and pain control only. She was also referred for an age-appropriate mammogram, osteoporosis screening, and hypercalcemia was overlooked. The patient was noncompliant with the referral and had delayed screening. Two weeks later the patient presented to the emergency department with worsening symptoms. Upon discharge, the patient presented for follow-up at our primary care clinic. On presentation, labs were reviewed and showed hypercalcemia since 2018 and current elevated serum calcium of 12.1 in addition to upper extremity weakness and numbness bilaterally.

	Calcium
Date of lab draw:	Reference range: 8.6-10.4 mg/dL
7/20/2018	10.3
11/3/2018	10.7
9/10/2020 0912	11.3
11/9/2020	11.3
11/9/2020	12.6

The patient was noted to have an elevated serum calcium level of 10.3 in 2018. Despite this, the patient had multiple office visits between specialists and primary care where hypercalcemia was not documented

Results of the previously ordered mammogram showed a 5 cm infiltrative solid mass in the right retro-areolar region of the right breast. MRI was reviewed as well which revealed lytic lesions on the cervical and thoracic spine with compression deformity likely due to metastatic breast mass. The patient was then referred to the emergency department for evaluation for neurosurgery consultation and IV dexamethasone. Confirmatory testing is shown below:



A: T2 MRI showing pathological compression off the C7 vertebral body with retropulsion add epidural tumor extension resulting in severe spinal canal stenosis.
B: T2 MRI thoracic showing widespread osseous metastatic disease without significant epidural tumor extension at the thoracic level. Mild to moderate wedging compression deformity and T7, without retropulsion.
C: T1 MRI lumbar showing widespread osseous metastatic disease.
D: Non-contrast CT showing large right breast mass reflecting breast cancer.

ER 70, PR <1, Ki 50, p53 neg, HER2 pos IHC 3+

Following the imaging results, the patient was placed on high-dose steroids and analgesics. The patient then required multiple surgeries for compression and stabilization of the spine, including anterior C7 corpectomy, titanium intrabody cage, arthrodesis, fusion using locally harvested autograft from C6 to T1, and C3-T1 laminectomies. Following surgery, pathology showed metastatic cancer involving fragments of bone, favoring mammary origin. Her PTHrP was further found to be negative. Chemotherapy for metastatic cancer was initiated by hematology-oncology. Endocrinology found that hypercalcemia was likely a component of metastatic humoral hypercalcemia as well as primary hyperparathyroidism. Lastly, the patient was treated with Zometa and calcitonin for hypocalcemia and eventually discharged home with frequent chemotherapy follow-ups.

Discussion

Hypercalcemia is common in patients with malignancy and is associated with potentially life-threatening sequelae [3]. Three mechanisms of hypercalcemia of malignancy (HCM) have been recognized: excessive production of parathyroid hormone-related protein (PTHrP), bony metastasis with the release of osteoclast activating factors, and production of 1,25-dihydroxy vitamin D (calcitriol) [2]. Although PTH-rP is the most common mechanism, bony metastasis tends to have the more debilitating symptoms such as cord compression and pathological fractures being the most feared [2].

Signs and symptoms of hypercalcemia include abdominal pain, muscle or joint pains, lethargy, bone pain, polyuria, nausea, vomiting constipation, headache, and psychiatric symptoms [1,3]. However, many patients with hypercalcemia are often asymptomatic leading to 35% of cases being missed [3]. Routine laboratory testing carried out during routine annual physicals has been shown to be effective in detecting up to 90% of asymptomatic hypercalcemia with (20-30%) being a result of underlying malignancy [2]. Calcium level also has to be adjusted based upon serum albumin levels by utilizing the following formula: serum calcium + 0.8 x (4 - patient's albumin level) as ionized calcium is bound by albumin.

Treatment of hypercalcemia of malignancy revolves around 2 principles: treatment of the underlying malignancy along with reduction of the serum calcium level [4]. Evidence-based therapies for management include intravenous crystalloid fluids with or without loop diuretics, bisphosphonates, calcitonin, gallium nitrate, and corticosteroids [5]. In cases of cancers such as lymphoma, which increases vitamin D, corticosteroids have been used successfully [4]. High calcium levels are associated with heart arrhythmias and nervous system problems, so symptoms should be addressed long before becoming a medical emergency [1,6].

Conclusion

In conclusion, 90% of cases of hypercalcemia are due to primary hyperparathyroidism and malignancy-induced hypercalcemia [2]. Malignancy remains the most common cause of hypercalcemia in hospitalized patients [2]. While most cases are managed as outpatients, severe hypercalcemia requires inpatient treatment [2]. Patients with uncontrolled malignancy and severe hypercalcemia have a poor prognosis [2]. Therefore, it is important to further evaluate asymptomatic hypercalcemia in an outpatient setting.

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