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Hypercalcemia in Malignancy; the Second Great Masquerader

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Authors' contributions

This work was carried out in collaboration between all authors. Author AHM designed the study and wrote the protocol. Authors AHM, MQM and MS managed the literature searches. Authors AHM, MS, JVU, AJ and MQM wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Case Study

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ABSTRACT

Hypercalcemia in malignancy can present with metabolic derangement, generalized weakness, altered mental status, renal compromise, cardiac dysrhythmias including atrial fibrillation and bradycardia, abdominal pain and/or shortness of breath amongst many other clinical manifestations. We present three cases of hypercalcemia in patients with malignancies; followed by discussion of hypercalcemia including etiology, clinical presentation and treatment.

Keywords: Hypercalcemia; malignancy; cancer; clinical manifestations; management, dysrhythmia.

1. CASE PRESENTATIONS

1.1 Case 1

This is a 61-year-old male with a history of a treated nasopharyngeal diffuse large B-cell lymphoma. He had a clinical course that was complicated by neutropenic fever requiring a

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hospitalization for pneumonia, pulmonary embolism, and new-onset rapid atrial fibrillation to 120 beats per minute (bpm). During the hospitalization, metoprolol and amiodarone were initiated for atrial fibrillation. An echocardiogram showed left ventricular dysfunction with an ejection fraction (EF) of 45-55%, which was decreased compared to an echocardiogram done prior to chemotherapy, showing an EF of 55-65%. He converted back to normal sinus rhythm (NSR) the next day and was discharged on lisinopril, furosemide, metoprolol and enoxaparin. He was eventually transitioned to warfarin.

Lab work drawn approximately every 3 months showed normal serum calcium and albumin levels, with the last value being drawn about one month prior to presentation in our emergency center (EC).

He underwent a biopsy of a suspicious liver lesion, which was positive for lymphoma. In preparation for that procedure, his warfarin had been stopped about 1 week prior. Lab work done on the day of the biopsy was limited to prothrombin time (PT) of 13.6 seconds, an international normalized ratio (INR) of 1.02, a normal complete blood count (CBC) and a serum creatinine (S_{Cr}) of 1.02 mg/dL. He presented to the EC with increasingly severe weakness, nausea, vomiting and mild abdominal pain and a low-grade fever to 100.2º F (37.8ºC) at home, with all symptoms beginning after the liver biopsy. He denied having diarrhea, chest pain, or shortness of breath. On physical exam (PE), he was well-developed, in no distress, but appeared weak. His vital signs on presentation included a blood pressure (BP) of 158/81 mmHg, a heart rate (HR) of 82 beats per minute (bpm), a respiratory rate (RR) of 16 breaths per minute, and a temperature of 98.6º F (37ºC). He had an oxygen saturation of 99% on room air. His PE was otherwise unremarkable, including his abdominal, cardiopulmonary exams, and his mental status. Lab work was significant for a blood urea nitrogen (BUN) level of 34 mg/dL (up from 12 mg/dL about one month before), a S_{Cr} level of 1.57 mg/dL (increased from a prior level of 0.83 mg/dL one month before), a carbon dioxide level of 39 mEq/L (up from 29 mEq/L one month before), and a calcium level of 18.8 mg/dL (up from 9.2 mg/dL one month before). His serum phosphorus level was 3.5 mg/dL, in normal range. The calculated corrected serum calcium level was 19.0 mg/dL and other labs and urinalysis were non-contributory. An abdominal x-ray series with a single-view chest x-ray were completed, showing no evidence of lung pathology, obstruction, ileus, or perforation, and no skeletal abnormalities. He was ultimately diagnosed with dehydration leading to renal insufficiency, contraction alkalosis and resulting severe hypercalcemia. He was started on vigorous hydration with normal saline, 2.5 liters initially then continued at 125 mL per hour. A confirmatory ionized calcium level completed was 9.6 mg/dL (normal range 4.48-5.28 mg/dL), so the patient was also given a dose of zoledronic acid 4 mg infused intravenously over fifteen minutes, and the patient was admitted to the hospital. Labs were rechecked and the serum calcium was 17.1 mg/dL. The BUN and S_{Cr} were essentially unchanged at 35 mg/dL and 1.53 mg/dL. His CBC including hemoglobin was stable compared to baseline values.

The primary (Lymphoma) service provider assessed the patient and an MRI of the brain was ordered due to lethargy, vomiting and a suspicion for brain metastases and he given a dose of calcitonin; 700 units (approximately 8 units/kg). An initial electrocardiogram (ECG) was completed that showed normal sinus rhythm with a heart rate of 84 bpm, non-specific T-wave flattening and U-waves, and a QT_C of 421 msec. A troponin level was ordered which was 0.00 ng/mL.

He was later noted to be confused with slurred speech and tachycardic to 165 bpm. The physician on duty was called to the bedside to evaluate the patient. His blood pressure was

111/71 mmHg, and pulse oximetry was normal. He denied chest pain, shortness of breath, and abdominal pain. On PE, he was not in acute distress and had clear lungs and a nontender abdomen, but had *rapid irregularly irregular* heart sounds. He was confused, but oriented x 3, moved all 4 extremities symmetrically and no cranial nerve abnormalities were noted. An ECG revealed a rhythm of *rapid atrial fibrillation* with a response rate of 170 bpm. He was given intravenous diltiazem 20 mg x 2 doses with a transient response in heart rate. Diltiazem continuous infusion was initiated at 5 mg/hour, and subsequently, the patient was given an intravenous bolus of amiodarone 150 mg, and started on an amiodarone continuous infusion at 1 mg/min. At one point, he had a low BP of 80 mmHg (systolic), but this quickly responded to a 500 mL fluid bolus, and he had no further hypotensive episodes. His HR improved to 120 bpm within several hours of treatment.

Labs were rechecked that showed an ionized calcium of 8.0 mg/dL, a potassium level of 3.4 mg/dL and a magnesium level of 1.3 mg/dL (both below normal values). A set of cardiac enzymes (CEs) was negative, and subsequent CEs in the next 24 hours were also negative for myocardial damage.

The patient was eventually transported to the intensive care unit (ICU) and soon converted to normal sinus rhythm. His calcium was down to 14.1 mg/dL at that time. Calculated corrected calcium was now 15.1 mg/dL. Another confirmatory ionized calcium level checked and was down to 6.12 mg/dL. Of note, thyroid function tests including a free T4 level and thyroid stimulating hormone (TSH) were within normal range.

The remainder of his hospitalization was notable for continued improvement in his calcium levels, mental status, and abdominal pain. Hypercalcemia treatment was continued after initial treatment with zolendronic acid with normal saline hydration at 125 cc/hr and calcitonin 700 units SQ every 12 hours and his serum calcium level began to trend below normal range. By the sixth day, the corrected calcium level was 7.54 mg/dL. A confirmatory ionized calcium was 3.4 mg/dL, below normal range. Intravenous calcium gluconate replenishment was started and continued daily until discharge 6 days later when his corrected calcium level was 7.54 mg/dL. He developed hospital-acquired pneumonia and a peripherally inserted central catheter (PICC) line-associated upper extremity venous thromboembolism, and was kept in the hospital. He did well on intravenous antibiotics and anticoagulation with enoxaparin. His MRI of the brain done on day 1 of his hospitalization revealed new calvarial lesions, and no evidence of brain metastases. A subsequent bone marrow biopsy performed in the iliac crest confirmed the diagnosis of B-cell lymphoma with bony invasion. The patient was started on systemic and intrathecal chemotherapy and was then discharged 16 days after admission. At this time, his kidney function had also improved (BUN and S_{Cr} were 18 mg/dL and 1.0 mg/dL, respectively).

1.2 Case 2

A 64-year-old male presented to our EC seeking care for shortness of breath, hemoptysis, delirium episodes and weakness, increasing over 3 days. He previously presented at another hospital earlier that month with weight loss, anorexia, cough and acute rib pain that was found to be due to a pathological rib fracture. There, he had abnormal findings on a chest x-ray and computed tomography (CT) scan of the chest suggesting malignancy, and subsequent biopsy of a supraclavicular lymph node revealed squamous cell lung cancer. He was informed that it was stage 4 with bony metastases and that he was not eligible for chemotherapy due to poor performance status in the setting of advanced disease. His family arranged for an outpatient consultation at our cancer center, but 3 days prior to presentation

in our EC, he started having the acute symptoms noted above. There was no report of fever, vomiting, diarrhea, abdominal pain, chest pain, urinary symptoms, rash or headache. His only past medical history included hypertension, and his social history included heavy smoking. In the EC, his vital signs were as follows: BP of 109/72 mmHg, HR of 113 bpm, RR of 24 breaths per minute, temperature of 97.5º F (36.4ºC), and an oxygen saturation of 94% on room air. He was described as cachectic, appearing to be short of breath and having pain in his ribs and lower spine. His PE was significant for crackles and rhonchi bilaterally on lung exam, tachycardia on heart auscultation, with the remainder otherwise unremarkable. Various diagnostic tests were checked in the EC, which included blood cultures, lactic acid, CBC, metabolic profile, liver function tests, urinalysis and urine culture, and a chest x-ray. Levalbuterol and ipratropium nebulizer treatments were also initiated. A one-liter normal saline bolus was given, and then IV fluids were maintained at 100 mL/hour. The chest x-ray showed a right lower lobe opacity concerning for pneumonia. His lab work showed a white blood count (WBC) of 14.1 10^9 /L, a BUN level of 32 mg/dL, S_{Cr} of 1.23 mg/dL, and a lactate level of 4.6 mmol/L. His serum calcium was 17.5 mg/dL (corrected calcium level of 17.7 mg/dL). Other labs and diagnostics including a phosphorus level and urinalysis were noncontributory. When the calcium level was noted, a 2-liter bolus of normal saline was ordered, and he was given calcitonin 300 units subcutaneously (approximately 4 units/kg), hydrocortisone 50 mg intravenously, and zoledronic acid 4 mg intravenously infused over 15 minutes. An ECG was performed and read as normal. He was initiated on broad spectrum intravenous vancomycin and cefepime to empirically treat for suspected healthcare-associated pneumonia. He was admitted to the telemetry unit as a precaution for closer cardiac monitoring and was placed on continued hydration with normal saline at 125cc/hr, intravenous antibiotics, subcutaneous calcitonin, and scheduled intravenous hydrocortisone. The next morning a repeat S_{Cr} was 1.1 mg/dL, calcium level was determined to be 13.0 mg/dL, and ionized calcium was measured at 6.8 mg/dL. His lactate level decreased to 2.5 mmol/L. His last subsequent measured calcium level during this hospitalization was on day 4 at 11.5 mg/dL with an ionized calcium level of 5.92 mg/dL done at the same time. He had CT of brain, chest and abdomen showing right lung cancer and pneumonia, diffuse metastatic lymphadenopathy and extensive bony metastases to the ribs, scapulae, pelvis, vertebrae, and calvarium. His hospital course was remarkable for new-onset *rapid atrial fibrillation*, treated acutely with metoprolol 2.5 mg IV x 4 doses. The patient remained in *atrial fibrillation* with a heart rate varying between 110 and 150 bpm; he was asymptomatic. He was subsequently started on intravenous amiodarone, and converted back to normal sinus rhythm. He also developed left arm swelling due to extrinsic subclavian venous compression secondary to the tumor without DVT. He required pain control with a patient-controlled analgesia (PCA) pump, and had a palliative care evaluation resulting in a do-not-resuscitate (DNR) status and a discharge from our institution to hospice care.

1.3 Case 3

A 54-year-old female with metastatic intrahepatic cholangiocarcinoma and an internal biliary stent presented to our EC with increasing weakness for 2 weeks. Staging CT studies 2 months prior revealed cancer to both liver lobes as well as perihepatic area, but no bony metastases were seen. She also had chronic cancer-related abdominal pain and nausea with intermittent vomiting. Her home medications included scheduled pregabalin and supportive, as-needed medications such as hydromorphone, metoclopramide, ondansetron, and zolpidem. Of note, she was not on any beta blockers or calcium channel blockers. She was using opioids as well as an unprescribed, unsanctioned oral cannabis-based oil preparation. Her outpatient oncologist noted an elevated calcium level of 11.6 mg/dL, approximately 11 days prior to her EC presentation. At that time, she was advised to go to

an EC for treatment, but she declined. Her corrected calcium was calculated to be 11.8 mg/dL. On the day she was sent to our EC for treatment, she had presented to her primary oncologist who noted hypotension (BP of 82/53 mmHg) and mild icterus. Labs done at the clinic revealed a calcium level of 13.5 mg/dL (corrected calcium of 14.1 mg/dL), and a total bilirubin of 1.9 mg/dL, which was higher than previous levels. In the EC, her vital signs were as follows: BP of 70/47 mmHg, HR of 68 bpm, RR of 18 breaths per minute, temperature of 96.7º F (36.3ºC), and an oxygen saturation of 96% on room air. On her initial PE, she was described as pale and toxic-appearing, but otherwise without remarkable abnormalities. She was placed on a telemetry monitor and a sepsis work-up was initiated including blood cultures, a normal saline bolus of 1 liter followed by continuous infusion at 125 ml/hr, and intravenous doses of vancomycin and cefepime. Her initial point-of-care (POC) lactate level was 1.53 mmol/L, and POC ionized calcium was 6.92 mg/dL (normal range 4.48-5.28 mg/dL). Her subsequent laboratory values were remarkable for hypercalcemia with a calcium level of 12.9 mg/dL (corrected calcium of 13.4 mg/dL), a phosphorus level of 3.1 mg/dL, a potassium level of 3.4 mg/dL, and elevated liver function tests (LFTs) including a total bilirubin of 1.5 mg/dL, direct bilirubin of 1.1 mg/dL, aspartate aminotransferase of 57 IU/L, alanine aminotransferase of 67 IU/L, and an alkaline phosphatase of 483 IU/L. Her CBC showed a WBC of 4.9 $X10^9$ /L and a hemoglobin of 9.6 g/dL. A dose of calcitonin 250 units (approximately 4 units/kg) was given, as was potassium chloride 40 mEq by mouth.

Her initial ECG showed a rate of 60 bpm with normal intervals, and a chest x-ray and urinalysis were non-contributory. She was diagnosed with hypercalcemia, dehydration, biliary obstruction due to a malfunctioning biliary stent, and possible sepsis. The decision to initiate bisphosphonate therapy with zoledronic acid was deferred to the primary admitting team.

With hydration, her BP improved to 107/57 mmHg, but her HR became much slower at 45-50 bpm, with a brief period where it decreased to 28 bpm (the patient remained conscious with a pulse during this time). She was admitted to a telemetry bed, evaluated by cardiology and treated for her hypercalcemia, as this was thought to be the cause of her *bradycardia*. A urine toxicology screen showed other drugs except hydromorphone. She also had a parathyroid hormone related peptide (PTHrP) level ordered that was high at 5.8 mmol/L and an intact parathyroid hormone (iPTH) level that was low at 4 pg/mL, ruling out primary hyperparathyroidism as the cause for the hypercalcemia.

A biliary catheter exchange was performed the next day. Throughout her hospitalization, the patient continued to receive subcutaneous calcitonin (4 doses total) every 12 hours and intravenous hydration with normal saline at 125 mL/hour, and she was discharged on 2 days after admission with a calcium level of 10.2 mg/dL and ionized calcium of 5.2 mg/dL (both within normal range). Upon discharge, her HR was 74 beats per minute and her BP was 123/61 mmHg. She did not receive any bisphosphonate therapy prior to discharge.

She subsequently saw her oncologist again 5 days later for right upper quadrant pain, which was uncontrolled since she was not prescribed opioids on discharge. She was noted to be very lethargic and her calcium level was 15.5 mg/dL (corrected calcium of 15.7 mg/dL, ionized calcium of 8.2 mg/dL), both higher than previous values. She was again sent to our EC for treatment. There, her vital signs were normal, and the PE was relatively unremarkable except for a general ill appearance and somnolence. EKG showed normal sinus rhythm. Her lab values were notable only for the hypercalcemia which was again treated with intravenous hydration, calcitonin 250 IU subcutaneously and a dose of zoledronic acid 4 mg intravenously over 15 minutes. She was discharged 4 days later with a

calcium level of 9.1 mg/dL (ionized calcium of 4.68 mg/dL). A new pleural effusion requiring a thoracentesis extended her length of hospital stay.

2. DISCUSSION

Hypercalcemia affects between 10% and 30% of patients with cancer [1]. Hypercalcemia is the most common life-threatening metabolic condition in advanced cancer patients and is associated with a median survival rate of 3 to 4 months [2]. In patients with hypercalcemia due to metastatic disease, the prognosis is poor [3]. In fact, in this population with hypercalcemia of malignancy, the survival is often less than 3 months and only 20% will survive twelve additional months from the initial episode of hypercalcemia [4].

The most frequently affected malignancies with hypercalcemia are multiple myelomas, breast, and lung cancers [5]. Multiple myelomas are characterized by diffuse skeletal infiltration and advanced breast cancer is characterized by multiple bone metastases. Further, humoral hypercalcemia of malignancy (HHM) characterizes some lymphomas, and solid tumors such as breast, squamous cell carcinomas of the head and neck, lung, kidney, and cervix uteri as they excrete various factors (such as parathyroid hormone-related protein, PTHrP) that indirectly increase serum calcium [5-8]. Hypercalcemia can be treated effectively if diagnosed, and if not, can lead to significant morbidity and be potentially fatal.

Multiple etiologies for hypercalcemia of malignancy have been described, and their incidence can vary based on cancer type. In the majority of cases, parathyroid hormone-related protein (PTHrP) is secreted by cancer cells, which mimics the action of parathyroid hormone (PTH). Stimulation of PTH receptors on the bones and kidneys increases bone resorption via osteoclastic activity and renal tubular reabsorption of calcium [9,10]. This mechanism is seen primarily in breast and lung cancers [5]. Another cause of hypercalcemia is osteolytic hypercalcemia, usually from metastases to the bones. This occurs when local metastatic destruction of the bones produces cytokines that increase osteoclast activity, which in-turn raises the serum calcium level. A third mechanism can be seen in some lymphomas. These lymphomas mediate increased production of 1, 25 – dihydroxycholecalciferol, causing an increase in serum calcium through increased absorption of calcium from the GI tract. Rarely, cancer can modify calcium regulation by causing ectopic secretion of parathyroid hormone [5,11]. Parathyroid hormone then goes on to exert its effect on bones and kidneys through increased bone resorption, increased renal reabsorption, as well as increased intestinal calcium reabsorption [5]. Concurrently, any combination of these mechanisms can cause hypercalcemia in malignancy. In our third case, there were direct measurements of the patient's intact parathyroid homone (iPTH) and parathyroid hormone related peptide (PTHrP) levels. Since the latter was elevated, that patient's etiology was due to tumor factor excretion. The first and second case patients did not have these levels measured, though both had bone metastases, so their etiology was likely multi-factorial. The first patient had lymphoma with only skull metastases, and since the lymphoma has subsequently gone into remission and he has been transplanted with stem cells, there had been no recurrence of hypercalcemia, implying that tumor related factor excretion was the prominent cause. The second patient had extensive skeletal metastases, likely making this his prominent mechanism of hypercalcemia.

The severity of symptoms due to hypercalcemia reflects both the calcium level as well as the rate of rise of the serum calcium [5,11]. Symptomatic hypercalcemia is more likely to be present when corrected calcium levels exceed 12.5 mg/dL. When calcium levels exceed 14 mg/dL, severe volume depletion, acute kidney injury, hypotension, and electrocardiographic

changes may ensue [12,13]. Clinical manifestations of hypercalcemia may include mild symptoms such as fatigue and lethargy, mental dullness, weakness, anorexia, polydipsia, polyuria, nausea, vomiting, abdominal pain and constipation; or more severe symptoms such as delirium, confusion, dehydration, and coma; as well as more rare manifestations like bradycardia, a shortening of the QTc interval, wide T-waves, cardiac arrhythmias, and a prolonged PR interval [5,14]. These cases reported were related in that they were all complicated by dysrhythmias. Our first and second cases showed patients who had *rapid atrial fibrillation* brought on most likely by hypercalcemia. In contrast, the third case presented shows a patient who had profound *bradycardia* associated with her hypercalcemia. Of course, these clinical scenarios can be confounded by multiple factors such as concurrent chemotherapy, pain medication interventions, comorbidities, or the cancer itself.

Calcium presents in the serum predominately in one of two forms: either bound to the proteins albumin and globulin or ionized-unbound [15]. It usually exists in these two forms in equal amounts. However, only the ionized form is significant physiologically in calcium regulation [16,17]. If albumin levels are low, as in the majority of cancer patients, the balance of the distribution of calcium between these two forms may become unequal, thus, more existing in the ionized, unbound form [15]. This leads to an overall serum calcium level which may appear normal, when in fact the patient is hypercalcemic. Serum calcium concentrations should be adjusted for hypoalbuminemia [18,11]. There are many online calculators to aid with this, but if one wanted to do it by hand, a well-accepted formula is:

Corrected Ca = 0.8 x [4.0 - Albumin (g/dL)] + [measured Calcium (mg/dL)] [19]. In addition, many hospitals have assays for directly measuring ionized calcium.

Management of hypercalcemia should utilize active treatment modalities including fluid resuscitation, calcitonin, and intravenous (IV) bisphosphonates, depending on the acuity and severity of symptoms. Patients commonly require aggressive rehydration with several liters of IV fluids to correct volume depletion and dehydration. The amount of fluids given should be dictated by the degree of dehydration, as well as other comorbidities such as heart failure. Although loop diuretics have been recommended in the past for their calciuretic properties, this practice is largely based off of historical precedence and practice. Since patients with hypercalcemia typically present with severe dehydration, volume depletion, and acute kidney injury, loop diuretics should be reserved only for patients with volume overload [20,11]. Calcitonin should be used to acutely address symptomatic hypercalcemia, which is more likely to be present when corrected calcium levels exceed 12.5 mg/dL as stated above. Calcitonin is used in hypercalcemia because it inhibits osteoclast activity, inhibits GI calcium absorption and inhibits renal tubular reabsorption of calcium, promoting urinary excretion. It acts to oppose the actions of PTH and PTHrP. A major advantage of calcitonin is its quick onset of action (within a few hours), and the ability to be used for prompt symptom control in patients with hypercalcemia. Despite the early effects of calcitonin on lowering serum calcium levels, it is less effective over the long term compared to bisphosphonates. In our third case report, the patient presented again with worse hypercalcemia a week after she was not treated with a bisphosphonate on her initial hospitalization. The reduced effect is due to tachyphylaxis seen with continued administration of the medication for greater than 48 hours, due to receptor downregulation. Calcitonin is usually administered subcutaneously or intramuscularly, and side effects are minimal

Currently, *IV bisphosphonates* are also one of the first-line therapies for hypercalcemia of malignancy due to their long-term efficacy. Bisphosphonates inhibit the activity of osteoclasts

and therefore decrease bone resorption. They do not impact PTHrP or its effect on calcium reabsorption in the kidneys. Bisphosphonates bind to hydroxyapatite following absorption on the surface of the bone, and can remain bound there for weeks to months. Currently, only pamidronate and zoledronic acid are FDA-approved for hypercalcemia of malignancy [5,11]. A study by Major et al. [21] compared pamidronate to zoledronic acid and showed superior efficacy with zoledronic acid in terms of response rates, duration of normocalcemia, and time to normocalcemia [21]. All our patients were treated with zoledronic acid. Bisphosphonates are poorly absorbed orally and thus are commonly given intravenously for this indication. Adverse effects of bisphosphonates include renal failure, which occurs more frequently with repeated dosing and shorter infusion times, osteonecrosis of the jaw, and transient flu-like symptoms [22,10,23]. One major advantage of bisphosphonate therapy is the long duration of action (approximately 1-4 weeks); however, their onset of action is delayed compared to other therapies [4]. A decrease in calcium levels is usually seen within 2-4 days with the nadir occurring within 4-7 days [11]. Some patients may require chronic treatment with periodic doses of zoledronic acid. It is recommended to wait at least 1 week to repeat a dose of this medication. There is also a known risk (about 10%) of inducing delayed hypocalcemia with this medication in patients who are treated for any indication. However, the incidence of this in patients treated for hypercalcemia with zoledronic acid is not well known. Our first patient had to have replenishment of his calcium daily until discharge and even so had low levels on discharge. Care should be given to monitor for this complication.

Historically, glucocorticoids were embraced as treatment for acute hypercalcemia. They lower calcium via decreased synthesis of 1,25-dihydroxyvitamin D and increasing urinary calcium excretion in some, creating a negative calcium balance. They continue to play a role in the treatment of hypercalcemia, particularly in multiple myeloma and lymphomas [24-28]. This treatment was used in treating our second case in addition to the calcitonin and zoledronic acid.

Therapies currently under investigation include denosumab, hydroxychloroquine and ketoconazole. Denosumab is a human monoclonal antibody directed at RANKL, a central stimulator of osteoclast activity. It is currently approved for osteoporosis and for the prevention of skeletal-related events in malignancy, but case reports and current studies are evaluating its role in hypercalcemia [29-31]. Like zoledronic acid, Denosumab has been associated with delayed hypocalcemia when used to prevent skeletal related events of malignancy. It is however far less likely to cause renal failure. Hydroxychloroquine and ketoconazole inhibit 1-α hydroxylase enzyme that converts 25-hydroxy vitamin D to the more active 1, 25-dihydroxy vitamin D. Inhibition of this pathway therefore decreases serum calcium levels [32].

Additional important considerations for treatment of hypercalcemia of malignancy include treating the underlying tumor, ruling out other causes for hypercalcemia (i.e. hyperparathyroidism or medication-induced), encouraging weight-bearing activity, and limiting exogenous calcium intake. Hemodialysis using a calcium-free dialysate can also be considered for severely symptomatic cases in the setting of acute kidney injury [11].

3. CONCLUSION

The main learning points we wished to illustrate in this review are as follows:

1. Hypercalcemia of malignancy can present with many varied signs and symptoms, including lesser-known ones such as abdominal pain and cardiac dysrhythmias.

2. The overall goal in treating hypercalcemia of malignancy is to alleviate symptoms and complications and reduce calcium levels by correcting dehydration, inhibiting osteoclast bone resorption, GI absorption and renal reabsorption, and ultimately correcting the underlying cause if possible. Bisphosphonates such as zoledronic acid are very effective and will help prevent recurrence of hypercalcemia, though rehydration and calcitonin will work faster. It is probably wise to use all 3 modalities to treat symptomatic patients if possible. In the future, Denosumab may become more common as a treatment since it does not cause renal failure.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Watson M, Lucas C, Hoy A, Wells J. Oxford handbook of palliative care. Oxford University Press; 2009.
2. Bower M, Cox S. Endocrine and metabolic complications of advanced cancer. Oxford Textbook of Palliative Medicine. 2004;688-690.
3. Makras P, Papapoulos SE. Medical treatment of hypercalcaemia. Hormones (Athens). 2009;8(2):83-95.
4. Twycross R, Wilcock A, Toller CS. Symptom management in advanced cancer palliativedrugs.com. Nottingham, United Kingdom; 2009.
5. Clines GA. Mechanisms and treatment of hypercalcemia of malignancy. Curr Opin Endocrinol Diabetes Obes. 2011;18(6):339-346.
   DOI: 10.1097/MED.0b013e32834b4401.
6. Santarpia L, Koch CA, Sarlis NJ. Hypercalcemia in cancer patients: Pathobiology and management. Horm Metab Res. 2010;42(3):153-164. DOI: 10.1055/s-0029-1241821.
7. Seymour JF, Gagel RF. Calcitriol: The major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. Blood. 1993;82(5):1383-1394.
8. Uno H, Shima T, Maeda K, Katakami H, Tsubouchi H. Hypercalcemia associated with parathyroid hormone-related protein produced by B-cell type primary malignant lymphoma of the kidney. Ann Hematol. 1998;76(5):221-224.
9. Heatley S. Metastatic bone disease and tumour-induced hypercalcaemia: Treatment options. Int J Palliat Nurs. 2004;10(1):41-46.
10. Lumachi F, Brunello A, Roma A, Basso U. Medical treatment of malignancy-associated hypercalcemia. Curr Med Chem. 2008;15(4):415-421.
11. Stewart AF. Hypercalcemia associated with cancer. N Engl J Med. 2005;352(4):373-379. DOI: 10.1056/Nejmcp042806.
12. Nishi SP, Barbagelata NA, Atar S, Birnbaum Y, Tuero E. Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction. J Electrocardiol. 2006;39(3):298-300. DOI: 10.1016/j.jelectrocard.2005.10.015.
13. Ziegler R (2001) Hypercalcemic crisis. J Am Soc Nephrol 12 (suppl 1):S3-S9
14. Woodruff R. Palliative medicine: Evidence-based symptomatic and supportive care for patients with advanced cancer. Oxford University Press, USA. 2004.

15. Higgins C. Understanding laboratory investigations for nurses and health professionals. Wiley-Blackwell; 2007.
16. Favus MJ, Goltzman D. Regulation of calcium and magnesium. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 2008;104.
17. Moore EW. Ionized calcium in normal serum ultrafiltrates and whole blood directly determined by ion-exchange electrodes. J Clin Invest. 1966;45(6):1047.
18. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J. 1973;4(5893):643-646.
19. Agraharkar M. Hypercalcemia, Medscape. http. Emedicine medscape com/article; 2008.
20. LeGrand SB, Leskuski D, Zama I. Narrative review: Furosemide for hypercalcemia: An unproven yet common practice. Ann Intern Med. 2008;149(4):259.
21. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. J Clin Oncol. 2001;19(2):558-567.
22. Ashley C, Currie A. The renal drug handbook. Radcliffe Medical Press, Oxford; 2009.
23. Samphao S, Eremin J, Eremin O. Oncological emergencies: Clinical importance and principles of management. European Journal of Cancer Care. 2010;19(6):707-713.
24. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary Dexamethasone Treatment of Multiple-Myeloma. Blood. 1992;80(4):887-890.
25. Frankfurt O, Rosen ST. Mechanisms of glucocorticoid-induced apoptosis in hematologic malignancies: Updates. Curr Opin Oncol. 2004;16(6):553-563. DOI: 10.1097/01.cco.0000142072.22226.09.
26. Hosking DJ, Stone MD, Foote JW. Potentiation of calcitonin by corticosteroids during the treatment of the hypercalcaemia of malignancy. Eur J Clin Pharmacol. 1990;38(1):37-41.
27. Kristensen B, Ejlertsen B, Holmegaard S, Krarup-Hansen A, Transbøl I, Mouridsen H. Prednisolone in the treatment of severe malignant hypercalcaemia in metastatic breast cancer: a randomized study. J Intern Med. 1992;232(3):237-245.
28. Ralston SH, Gardner MD, Dryburgh FJ, Jenkins AS, Cowan RA, Boyle IT. Comparison of amino hydroxyl propylidene diphosphonate, mithramycin, and corticosteroids/calcitonin in treatment of cancer-associated hypercalcaemia. 1985;2(8461):907-910. Lancet.
29. Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M, Holloway D, Peterson MC, Bekker P. A study of the biological receptor activator of nuclear factor-kappa B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res. 2006;12(4):1221-1228. Doi: 10.1158/1078-0432.Ccr-05-1933.
30. Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, Gao G, Wu L, Sohn W, Jun S. Randomized Phase II Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates. J Clin Oncol. 2009;27(10):1564-1571.

    DOI: 10.1200/Jco.2008.19.2146.

31. Hu MI, Glezerman I, Leboulleux S, Insogna K, Gucalp R, Misiorowski W, Yu B, Ying W, Jain RK. Denosumab for Patients with Persistent or Relapsed Hypercalcemia of Malignancy Despite Recent Bisphosphonate Treatment. Jnci-J Natl Cancer I. 2013;105(18):1417-1420. DOI: 10.1093/Jnci/Djt225.

32. Conron M, Young C, Beynon HLC. Calcium metabolism in sarcoidosis and its clinical implications. Rheumatology. 2000;39(7):707-713. DOI:10.1093/rheumatology/39.7.707

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