Case Report

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A 65-Year-Old Man with Parathyroid Independent Hypercalcemia Due to Renal Cell Carcinoma and Resolution of Hypercalcemia Following Nephrectomy; Proposed Mechanisms of Hypercalcemia With Renal Cell Carcinoma

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ABSTRACT

We report a case of a 65-year-old man who presented to the Endocrine service for hypercalcemia. He had painful joints, muscle aches, joint stiffness, and incidentally discovered elevated calcium levels on two separate occasions. A lab evaluation indicated non-parathyroid mediated hypercalcemia with calcium levels in the range of 10.1-10.5mg/dl. Parathyroid hormone related peptide (PTHrP) level was undetectable. His PTH and 25-OH Vitamin D levels were normal. But his 1, 25 Dihydroxy Vitamin D levels were low. Initial imaging revealed a heterogeneously enhancing mass on the posterolateral left kidney. Our patient underwent a left nephrectomy, and the mass was identified as RCC on surgical pathology. We illustrated the differential diagnosis of hypercalcemia and the evaluation of hypercalcemia occurring with RCC. This case explains that we need to carefully evaluate, interpret, and review all the data, especially when the patient has borderline elevated calcium levels and does not have a typical presentation of malignancy.

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Introduction

Among the genitourinary cancers, Renal Cell Carcinoma (RCC) has the highest mortality rate, and the incidence of RCC has increased steadily [1]. Once detected early, RCC is curable by surgery, although some are at risk of recurrence [2]. An aging population and an increase in incidental detection have led to active surveillance as an option for patients with small renal masses [3]. RCC encompasses many histological and molecular subtypes, of which clear cell variety is most common and accounts for most cancer-related deaths [4]. Although the cause of RCC is not well understood, certain factors increase the risk of renal cancer, e.g., old age, African American, hypertension, obesity, renal failure, dialysis, polycystic kidney disease, sickle cell disease, renal stones, workplace exposure to certain substances like cadmium, asbestos, certain herbicides and trichloroethylene and certain hereditary diseases (tuberous sclerosis, Von Hippel-Lindau syndrome, hereditary papillary renal carcinoma, and hereditary leiomyomatosis and renal cell carcinoma (HLRCC)) [1,5]. Signs and symptoms of RCC such as back pain, abdominal mass, and hematuria result from either a direct tumor invasion of tissues or by its metastases [6,7]. In comparison, other signs and symptoms result from biologically active substances secreted by the tumor or by benign tissues in response to the tumor or via modulation of the immune system [6,7,8]. This clinical constellation of signs and

symptoms termed paraneoplastic is essential to identify as they could be a harbinger of cancer recurrence or the first presenting sign of the tumor [7,8]. The paraneoplastic syndromes associated with RCC range from fever, cachexia, and weight loss, to specific metabolic and biochemical abnormalities (i.e., hypercalcemia, erythrocytosis, hypertension, increased gonadotropins, increased prolactin, impaired glucose metabolism, polymyalgia rheumatica, non-metastatic hepatic dysfunction, amyloidosis, other hematological and neurological syndromes) [8,9]. In a patient presenting with renal cell carcinoma, the presence of a paraneoplastic syndrome is neither a marker of metastatic disease nor necessarily indicative of a poor prognosis. Since paraneoplastic syndromes may be produced by early, localized, and potentially curable disease, it is vital not to confuse them with metastatic spread. Proper evaluation and treatment of the tumor often lead to improvement or resolution of the paraneoplastic features [8,9].

Hypercalcemia is the most common paraneoplastic manifestation of RCC, accounting for 14-20% of the cases [10,11]. Elevated Calcium levels can cause a wide range of signs or symptoms, but sometimes one might not even know they have abnormal levels until routine blood tests reveal a high level of blood calcium [10,11,12]. More-severe cases with hypercalcemia often produce signs and symptoms related to the parts of the body affected by

elevated calcium levels in the blood, e.g., Excess calcium makes the kidneys work harder to filter it, which can cause excessive thirst and frequent urination; GI complaints like abdominal pain, nausea, vomiting, and constipation; Excess calcium in the blood can also get leached from bones, which weakens them causing bone pain and muscle weakness. Raised levels can also interfere with how the brain works, resulting in confusion, lethargy, fatigue, and depression. Sometimes, hypercalcemia can even interfere with heart function, causing palpitations and fainting, indications of cardiac arrhythmia, and other heart problems. The reference range of serum calcium levels varies among laboratories but generally is 8.4-10 mg/dl. Approximately 50% of calcium is bound to protein, primarily albumin, and the remaining 50% is ionized and is in physiologically active form. Mild elevations in calcium levels are usually asymptomatic and typically discovered on routine laboratory diagnostic testing (usually up to 11.5 mg/dL). When calcium levels are abnormal, the next step is to measure the albumin level, followed by calculating the corrected calcium level and the ionized calcium as well [9-15].

Hypercalcemia is a condition that most commonly results from malignancy or primary hyperparathyroidism. Other less common causes of elevated calcium include increased intake or absorption, hyperthyroidism, Familial hypocalciuric hypercalcemia, granulomatous disease, immobilization, and medications (thiazide diuretic, retinoids, lithium) [8,13-15]. However, the primary diagnostic approach should be first to rule out underlying malignancy and parathyroid disease[8,13]. There are four broad categories to classify hypercalcemia of malignancy: local osteolysis secondary to metastatic cancer or multiple myeloma, excess parathyroid-related hormone (PTHrP), excess 1, 25-dihydroxy vitamin D production, and ectopic parathyroid hormone production. Traditionally, humoral hypercalcemia of malignancy is due to the overproduction of PTHrP or 1,25VitD3 levels. However, other cytokines have also been discovered to cause hypercalcemia, e.g., Interleukin-6, prostaglandins, and TNF-alpha [8,13-15].

In our case, an older man presented with muscle aches, joint pains, and raised calcium levels on lab evaluation, who was later diagnosed with Renal cell carcinoma and underwent nephrectomy for the same, leading to resolution of his hypercalcemia.

Case Presentation

A 65- year-old man was referred to our endocrinology services due to his elevated blood calcium (Ca) levels on two separate occasions and normal parathyroid hormone levels on the second visit to his primary care physician. At the time of presentation, he reported having fatigue, weight gain, muscle aches, joint pains, joint stiffness, and excess sweating. He has chronic aches and pains b/c of his profession. He has a significant medical history of borderline Hypertension, Angina, Coronary artery disease, and type 2 DM but no history of hip fractures, kidney stones, osteoporosis, or any personal /family history of calcium disorders. There is a family history of diabetes in both the parents and heart disease in his mother. He quit smoking 15 years back and has no significant history of alcohol abuse. Though he was not on any calcium supplements, Thiazides, Lithium, or any other meds that could increase Ca level, he has been taking Enteric coated Aspirin tab 81mg once daily, Tablet Plavix 75 mg once daily, Tab Metoprolol Succinate extended-release 100mg once daily, Tablet Lisinopril 20mg orally once a day, Tablet Lipitor 40mg orally once a day before bed, Tablet Metformin 1000mg 1 tablet orally twice a day, Tablet oxybutynin 5mg extended-release tablet orally once a day, Fish oil capsule 1200mg once a day,

Vitamin D3 capsule orally once a day. He was alert and oriented on clinical examination with no scalp lesions, thyromegaly, lymphadenopathy, edema, and clubbing. The EOM was intact, the lungs were clear to auscultation, no murmurs, the abdomen was soft and non-tender, and the deep tendon reflexes were symmetrical (2+). His vitals were stable, and his blood pressure was well controlled. After a detailed workup, his lab findings revealed elevated calcium (10.5mg/dl), reduced 1,25 DihydroxyvitaminD3 levels, elevated 24-hour urinary calcium but normal levels of Parathyroid hormone, Magnesium, and Phosphorus. Parathyroid hormone-related peptide levels were undetectable. In addition, his blood urea nitrogen levels (BUN), Creatinine (Cr), and BUN/Cr ratio were elevated. Blood glucose readings were slightly elevated but were previously in the desired range. Albumin, Globulins. A: G ratio, AST, ALT, Alkaline Phosphatase (ALP) levels, total proteins, CBC, sodium, and potassium levels were all in the normal range. Subsequently, a CT scan of the chest, abdomen, and pelvis was performed, which showed a 3.3cm heterogeneously enhancing parenchymal mass on the posterolateral left kidney, highly suspicious of RCC. Total body scan and the skeletal survey did not reveal any osteolytic lesions. He was given 2-3 liters of normal saline. A nephrectomy was planned and was operated for the same on 11/2019. Later the pathology findings revealed a 3.3 cm, clear cell type with Fuhrman's grade 2 with a staging of T1N0M0. Post-surgery he became hypocalcemic and required intravenous calcium infusion. He was then discharged four days later. Subsequently, when seen on his follow up endocrinology visits, his calcium and vitamin D returned to normal levels over 2-3 months. His BUN, Anion gap, BUN/Cr have also returned to normal, but the Creatinine levels are still elevated with decreased GFR. Follow up CT scan of the abdomen showed no recurrence of RCC. He is currently on Enteric coated Aspirin tab 81mg once daily, Atorvastatin 40mg Tablet orally once a day, Tablet Flomax 0.4mg capsule twice a day, Tab neurotin 300mg 2 capsules three times a day, Tablet Plavix 75 mg once daily, Tab Metoprolol Succinate extended-release 100mg once daily, Tablet Lisinopril 20mg orally once a day, Tablet Lipitor 40mg orally once a day before bed, Tablet Metformin 1000mg 1 tablet orally twice a day, Tablet trimethoprim-sulphamethoxazole twice a day, Tablet oxybutynin 5mg extended-release tablet orally once a day, Fish oil capsule 1200mg once a day, Vitamin D3 capsule orally once a day. He is feeling better but still continues to have mild musculoskeletal aches and pains. Medicine reconciliation was done, and he was advised on lifestyle modifications, including exercise and dietary habits. He is now stable enough to be transferred back to his primary care physician.

Discussion

In this case, the patient had fatigue, muscle aches, joint pains, and stiffness with elevated calcium, decreased 1,25 dihydroxy vitamin D, deranged renal function tests, high BMI, and a 3.3 cm heterogeneous left renal mass on imaging, making Renal Cell Carcinoma the most likely diagnosis.

Paraneoplastic syndromes (PNS) are defined as a collection of signs and symptoms occurring in cancer patients. It is clinically significant to recognize a PNS for the following reasons: (1) may lead to the diagnosis of a previously undetected neoplasm; (2) it can overshadow the clinical picture and lead to errors in diagnosing origin and type of primary tumor; (3) it can follow the clinical course of the underlying tumor and thus help in monitoring its evolution. It is important to note that the incidentally discovered raised calcium levels led us to Renal Cell carcinoma diagnosis, which was later confirmed to be a clear cell variant on histopathological examination[8,9,15]. Retrospectively, studies

have shown us that 28-36% of the cases of hypercalcemia are attributable to malignancy. Hypercalcemia is the most common paraneoplastic manifestation of RCC, and approximately 17% of patients develop hypercalcemia during the course of the disease [8,9,15,16].

It is reported that PTHrP is elevated in approximately 47% of patients with malignancy and hypercalcemia as it causes increased resorption of bone and renal calcium absorption by binding to the PTH/PTHrP receptor [8,9,17]. However, in our case, the PTHrP levels were undetectable.

His 24-hour urinary calcium was elevated, and he has no family history of any calcium related disorder making familial hypocalciuric hypercalcemia unlikely. However, the PTH levels and phosphorus were in the normal range. Also, 1,25 dihydroxy vitamin D levels were abnormally low, ruling out hyperparathyroidism and ectopic PTH secretion. The presence of lytic bone lesions was later ruled out by skeletal survey and total body scan. His serum albumin levels and sodium, potassium, and magnesium were normal. Renal function tests were deranged with raised Creatinine and BUN levels.

Medications are also a common cause of hypercalcemia. However, our patient had been on his prescribed medications for years, and none of them are commonly associated with hypercalcemia. Calcitonin, Thyroid function tests revealed no abnormality. He didn't have any history of immobilization or Total parental nutrition. Increased prostaglandins have been stated to cause hypercalcemia in patients with RCC as they increase bone resorption. In that case, NSAIDs would have been effective. Our patient was on aspirin for his coronary artery disease; therefore, prostaglandin induced hypercalcemia is unlikely.

Other cytokines like IL-6, IL-1, TGF beta, and TNF alpha have also been discovered to cause hypercalcemia. IL-6 mediated hypercalcemia appears to be multifactorial and unclear: (a) Some studies say it enhances tumor growth; (b) It can activate osteoclastic resorption of bone and acts synergistically when coexpressed with PTHrP; (c) It may cause hypercalcemia either directly or indirectly by increasing the action of PTHrP on the bone. In this case, we could not analyze the serum by ELISA and perform Immunohistochemistry for IL-6 and TNF alpha as the stains were not available.

Low Vitamin D levels, normal complete blood count, normal chest X-Ray and absence of lymphadenopathy rule out lymphoma and granulomatous diseases. Normal CBC, normal SPEP make multiple myeloma unlikely. Rare causes of hypercalcemia like adrenal insufficiency, acromegaly and pheochromocytoma were also ruled out. Since the RFTs were deranged with elevated BUN/Cr ratio, anion gap, Creatinine levels, and low GFR, we suspected paraneoplastic hypercalcemia due to Renal Cell Carcinoma. A CT scan of the chest, abdomen and pelvis was performed, which revealed a 3.3 cm heterogeneous mass with no evidence of metastasis on the PET scan. The presence of hypercalcemia in metastatic RCC indicates a poor prognosis, which is unlikely in our patient who had a localized tumor. Thus, the most reliable indicator is the tumor node metastasis staging.

Treatment of hypercalcemia often involves restoration of the volume status by normal saline, Diuresis, and Bisphosphonates (anti-resorptive agent) like zoledronic acid. Our patient however required only normal saline to maintain his calcium levels in the desired range. Besides, encourage mobility and restrict calcium intake. Frequently monitor urine and electrolytes, albumin, sodium,

magnesium, and potassium levels. Approximately 50% of the patients that undergo nephrectomy will revert to hypercalcemia.

Conclusion

Hypercalcemia is a common paraneoplastic complication in patients with RCC, but frequently it is an unusual presenting symptom. One should focus on whether the hypercalcemia is parathyroid dependent, malignancy-related, or medication-induced after initial evaluation of corrected calcium levels, albumin, and magnesium. Necessary lab investigations include PTH, PTHrP, 1,25dihydroxyvitamin D, Thyroid function tests. In cases where the cause of hypercalcemia is unclear, bone-resorbing cytokines could be present. In our case, we could not find the specific cytokine that caused the hypercalcemia. Evaluation of hypercalcemia should be continuously pursued in patients who have symptoms of paraneoplastic hypercalcemia. If the lab findings are not diagnostic, CT scan, bone scan, and PET-CT should be one to evaluate for lytic lesions or underlying malignancy. Primarily in a patient with hypercalcemia, it is crucial to restore the volume status and subsequently treat it with antiresorptive agents with constant monitoring of serum electrolytes and albumin levels. Finally, the majority of the cases of paraneoplastic hypercalcemia with RCC resolve with nephrectomy.

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