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A Hypercalcemic Patient With Malignancy, Hyperparathyroidism, Hypercalciuria and Vitamin D Overdose; Management and Brief Literature Review

Malignensi, Hiperparatiroidizm, Hipokalsiüri ve Yüksek Doz Vitamin D Kullanım Öyküsü Olan Hiperkalsemik Bir Hasta;Yaklaşım ve Kısa Literatür İncelemesi

Emin Murat Akbaş[1], Adem Güngör[2], Aysu Timuroğlu[3], Hünkar Ağgül[3], Nergis Akbaş[4]

[1] Erzincan Üniversitesi, Tıp Fakültesi, İç Hastalıkları Ana Bilim Dalı, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Erzincan
[2] Atatürk Üniversitesi, Tıp Fakültesi, İç Hastalıkları Ana Bilim Dalı, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Erzurum
[3] Erzincan Üniversitesi, Tıp Fakültesi, İç Hastalıkları Ana Bilim Dalı, Erzincan
[4] Atatürk Üniversitesi, Tıp Fakültesi, Biyokimya Ana Bilim Dalı, Erzurum

Özet

Hiperkalsemi, sık görülen bir medikal problem olup pek çok sebebi vardır. En sık rastlanılan sebepleri malign hastalıklar ve primer hiperparatiroidizmdir. Ek olarak granülomatöz hastalıklar, ilaçlara bağlı hiperkalsemi ve çeşitli endokrin hastalıklar da hiperkalsemiye sebep olabilir. Hiperkalseminin klinik prezantasyonu ve prognozu; hiperkalsemi gelişme hızı, hiperkalseminin şiddeti ve altta yatan sebeplere bağlıdır. Birçok hasta konstitüsyonel, nörolojik, gastrointestinal semptomlar ve renal hastalık semptom ve bulguları ile başvurabilirler. Ciddi hiperkalsemide, hızlı ve etkili bir tedavi hayat kurtarıcıdır. Raporumuzda, merkezimize hiperkalsemi ile başvurup; malignite, hiperparatiroidizm, hipokalsiüri, tiazid diüretiği ve aktif-inaktif D vitamini kullanımı gibi bir çok hiperkalsemi sebebi olan bir hastaya yaklaşımımızı ve literatür bilgisini sunmayı amaçladık.

Anahtar Kelimeler: Hiperklasemi, neoplazm, hiperparatiroidi, hipokalsiüri, vitamin D.

Abstract

Hypercalcemia is a common medical problem which has many causes. The most common causes of hypercalcemia are malignant diseases and primary hyperparathyroidism. Additionally granulomatous diseases, medications, endocrinological diseases may cause hypercalcemia. The clinical presentation and prognosis of hypercalcemia is related to the speed of development of hypercalcemia, underlying diseases and the severity of hypercalcemia. Most patients apply with constitutional, gastrointestinal and neurological symptoms or signs and symptoms of renal disorders. In patients with severe hypercalcemia, fast and effective therapy is essential. In this report, we aimed to discuss literature and management of a patient with hypercalcemia who has numerous etiologic factors for hypercalcemia as malign disease, hyperparathyroidism, hypocalciuria, usage of thiazide diuretic and active-inactive vitamin D.

Keywords: Hypercalcemia, neoplasm, hyperparathyroidi, hypocalciuria, vitamin D.

Introduction

Prevalence of hypercalcemia varies between 0.17% and 2.92% in the hospitalized population while it has been reported at surprisingly at high rates ranging in normal population between 1.07% and 3.9% (1). Hypercalcemia is a laboratory finding of a wide variety of conditions. Primary hyperparathyroidism (50%) and hypercalcemia associated with malignancies (30-40%) constitute about 90% of all hypercalcemias (2, 3). The remaining 10% of hypercalcemias are caused by granulomatous diseases, several drugs (thiazide diuretics, lithium, vitamins D and A, aluminum intoxication), endocrine disorders such as thyrotoxicosis, pheochromocytoma, and adrenal insufficiency, and other rarer diseases like familial hypocalciuric hypercalcemia (2).

Symptoms and findings depend on seriousness and duration of development of hypercalcemia. The patient may present with an asymptomatic, good clinical course or with a serious and even life-threatening condition. Neurological dysfunction is common and may manifest with a spectrum from mild cognitive impairment to unconsciousness. Muscular weakness, constipation, nausea, vomiting, polyuria, dehydration, peptic ulceration, pancreatitis, short QT interval, bradycardia, tachycardia, first degree atrioventricular block, cardiac dysrhythmias, uro-nephrolithiasis, nephrocalcinosis, osteopenia, and osteoporosis may be observed with hypercalcemia. The fact that symptoms and findings show diversity in the patients with hypercalcemia and that wide range of diseases play role in etiology may occasionally cause difficulty in diagnosing and managing the condition.

İletişim Bilgisi / Correspondence
Yard. Doç. Dr. Adem Güngör, Atatürk Üniversitesi Tıp Fakültesi Hastanesi, İç Hastalıkları Ana Bilim Dalı, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Erzurum
E-mail: drademgungor@gmail.com

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In the current case report, we present an interesting case with history of malignancy for whom history of use of high dose of active and inactive vitamin D and thiazide diuretic, and whose daily urinary calcium excretion has been reported to be low in two separate medical centers, and for whom hyperparathyroidism was reported.

Case Report

Ulcerative-vegetative mass was found in another medical center in a 65 years old man upon finding hoarseness which began 1 year ago and worsened 7 months ago. Biopsy of the patient with history of smoking of 40 packs per year revealed squamous cell carcinoma. Refusing operation, the patient received radiation therapy. At that time, elevated levels of urea and creatinine were found in the patient without known previous renal diseases. Glomerular filtration rate was calculated as 30 ml per minute and level of calcium (Ca) in 24 hour urine sample was found to be 10.2 mg/day.

Urinary system ultrasound examination revealed millimetric calculi in the left kidney and sizes of the kidneys were reported as 100 x 54 mm for the right kidney and 100 x 50 mm for the left kidney. Level of parathyroid hormone (PTH) was reported as 224.2 pg/mL, Ca level as 9.65 mg/dL, and phosphorus level as 3.2 mg/dL. Whole-body scanning revealed previous trauma on the right clavicle and scintigraphic findings due to degenerative arthritic changes in the sacroiliac joints and in the joints of the lower and upper limbs on both sides. Parathyroid scanning showed focal retention consistent with parathyroid adenoma adjacent to lower pole of the left thyroid lobe. Oral cholecalciferol (300.000 units/day for 5 days followed by 300.000 units/week for 4 weeks) was started 2 months before the patient was presented to our center. Subsequently, calcitriol 0.5 mcg twice daily was started by another physician and the patient was instructed to come back for follow-up 1 month later. The patient presented to our out-patient clinic for controls. The subject reported his complaints of drinking so much water, polyuria, and constipation started 1 month after he started taking his drug. Findings on the physical exam of the patient taking irbesartan + hydrochlorothiazide were as follows: general health status was intermediate; orienting and cooperating; blood pressure 140/80 mm/Hg; heart rate at the apex 84 bpm; respiratory rate 14 per minute; and fever 37.1 0C. The patient had hoarseness, skin and mucosal surfaces were dry and skin turgor was reduced. Laboratory findings were as follows: alkaline phosphatase: 57 U/L; TSH: 0.781 mIU/L, Ca: 13.4 (corrected Ca: 13.8) mg/dL; creatinine: 2.62 mg/dL, albumin: 3.5 g/dL; phosphorus: 2.8 mg/dL, PTH: 25 pg/mL, 1-25-dihydroxy vitamin D: 14 pg/mL, 25-hydroxy vitamin D: 88.5 ng/mL; Ca in 24 hour-urine: 42.9 mg/day. Ratio of calcium to creatinine clerence ([UCa×SCr] / [SCa×UCr]) was reported as 0.09. Other investigations of the patient were unremarkable.

He was admitted to the hospital with presumed diagnosis of vitamin D intoxication, acute renal injury on background of chronic renal disease, larynx cancer, bone metastases, and primary hyperparathyroidism. He was started hydration therapy with 0.9% NaCl solution. His anti-hypertensive medication was replaced with amlodipine. Central venous pressure was measured as 2 cm/H2O and it was elevated to 10 cm/H2O during his follow-up. Being followed in our clinic for 6 days, the patient's level of calcium reduced to 10.2 mg/dL and creatinine level reduced to 1.98 mg/dL with hydration therapy only. Hypercalcemia of the patient was attributed to use of high dose of active and inactive vitamin D and hydrochlorothiazide by excluding hypercalcemia associated malignancy, primary hyperparathyroidism, and familial hypocalciuric hypercalcemia upon lack of findings consistent metastasis on bone scanning, low ratio of calcium to creatinine clearance, and falling levels of PTH following replacement of vitamin D. Wishing to be discharged from the hospital, the patient was discharged with recommendations of oral hydration and coming back for control in the out-patient clinic. In his follow-up investigations level of PTH was 129.7 pg/mL, albumin 3.8 g/dL, creatinine 1.55 mg/dL, and calcium 9.6 mg/dL.

Conclusion

Calcium is an important cation playing many roles in several physiological processes. It is regulated in a narrow range in the circulation. Hypercalcemia occurs when amount of calcium from the gastrointestinal tract, kidneys, and skeleton exceeds capacity of renal calcium excretion. Hypercalcemia is a common metabolic disorder for which positive outcomes may be achieved through successful diagnosis and treatment (1, 2). Hypercalcemia has many causes that may be categorized in different groups with more than one cause being found in some of the cases of hypercalcemia.

In our case, cause of hypercalcemia was seen to be use of high dose of active and inactive vitamin D, one of the most significant causes of hypercalcemia. Vitamin D is commonly prescribed because it has been linked to many diseases beyond metabolic bone diseases and it is a current medical issue. Thus, Vitamin D intoxication has been reported more commonly and is usually due to the fact that the healthcare professionals prescribe it without a definitive diagnosis or that the person use it at inappropriate doses (4). Being one of the most important markers of Vitamin D intoxication, hypercalcemia occurs when level of Vitamin D exceeds 150 – 200 ng/mL but some observational trials claim that levels of vitamin D above 50 ng/mL increase mortality and morbidity (5, 6). In our case, level of 25-hydroxy vitamin D was found as 88, 5 ng/mL.

The fact that rate of calcium excretion in 24 hour urine was reported low in two center (10.2 and 42.9 mg/day) suggested the etiologies decreasing renal excretion. Among them, familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant condition which is due to mutation causing inactivation in the calcium-sensing receptors and characterized by mild/intermediate hypercalcemia, hypocalciuria, normal or mildly elevated level of parathyroid hormone (PTH). Its diagnosis is made by demonstrating hypocalciuria after exclusion of other causes of hypocalciuria. Ratio of calcium creatinine clearance is below 0.01 in 80% of the patients and combined with genetic tests, it increases diagnostic sensitivity to 98% (7). Genetic testing was not performed in our case but this presumed diagnosis became less likely because laboratory findings were inconsistent with the condition, the subject was not using thiazide diuretic, and ratio of calcium to creatinine clearance was calculated as 0.09. Use of thiazide diuretic is another cause of hypocalciuric hypercalcemia and due to reduced renal calcium excretion. Annual incidence of hypercalcemia associated with thiazide diuretics has been reported as 7.7 in 100.000 and the fact that hypercalcemia persists after discontinuing the diuretic in 64% of the patients suggests that another cause underlying the condition predisposes to hypercalcemia (8).

Hypercalcemia associated with malignancy is a clinical entity that may be be seen in 20 to 30% of the patients with malignancy and occurs through 4 main mechanisms: by making osteolytic bone metastases; by releasing PTH-like peptides; by releasing ectopic PTH, or by releasing 1-25(OH)2 vitamin D [2, 9]. Hypercalcemic conditions due to the last 3 of these mechanisms are referred as Humoral hypercalcemia of malignancy (MHH) and are responsible of 80% of hypercalcemic conditions associated with malignancy (9). Cases due to ectopic PTH release has been reported very rarely [9]. Laboratory findings overlap with those of primary hyperparathyroidism but no involvement typical for parathyroid adenoma is observed. In the current case, hypercalcemia associated with malignancy became less likely because bone metastases were excluded on the bone scannings, level of PTH was suppressed in the period of hypercalcemia when hyperparathyroidism was found before intake of high dose of vitamin D.

Considering the level of 25-hydroxy vitamin D at the time of presentation, the authors believe that hypercalcemia could not be explained solely by use of high dose of active and inactive vitamin D. It is believed in our case, combined use of aggressive treatment with vitamin D and thiazide diuretic started upon hyperparathyroidism due to possible vitamin D deficiency-chronic renal failure. Focal

retention found on the parathyroid scanning and indication possible parathyroid hyperplasia may have contributed to the process.

As with the current case, treatment with saline solution may suffice for correcting hypercalcemia along with treatment of the underlying etiological factors without further medication (2, 3). However, such therapeutic modalities as loop diuretics, biphosphonates, calcitonin, glucocorticoids, and hemodialysis should be added in the patents not responding to effective hydration.

Previous treatments should be queried prior to starting treatment with vitamin D. Level of vitamin D should be assessed and the conditions that may predispose to hypercalcemia should be reviewed. In order to avoid side effects, vitamin D should only be used cautiously in the case of indication. It should be kept in the mind that more than one factor may be involved in etiology of the cases with hypercalcemia.

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