Humoral hypercalcemia of malignancy in a patient with hypoparathyroidism

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Abstract. – INTRODUCTION, Elevated plasma calcium level in patients diagnosed with primary hypoparathyroidism is a rare finding, resulting in most cases from the treatment with excessive doses of either vitamin D or its derivatives, or calcium salts.

CASE, We report a case of a woman who developed severe hypercalcemia due to metastatic lung cancer, describing diagnostics strategies undertaken in this patient. Pamidronate treatment with subsequent chemotherapy resulted in a transient normalization of plasma calcium levels.

CONCLUSION, Our report shows that the presence of malignancy should always be taken into consideration in hypoparathyroid patients in whom plasma calcium levels increase and that the assessment of plasma levels of parathyroid hormone related peptide may be helpful in the differential diagnosis of hypercalcemia.

Key Words: Hypercalcemia; Hypoparathyroidism; Lung cancer; Parathyroid hormone-related protein; Diagnosis and treatment.

Introduction

Hypocalcemia is a characteristic feature of primary hypoparathyroidism, resulting from reduced production of parathyroid hormone (PTH)1. Elevated plasma calcium levels in individuals suffering from this disorder have been observed to date in only several patients. In most hypoparathyroid patients, abnormally high calcium levels were secondary to either treatment with excessive doses of vitamin D or vitamin D derivatives, or to intake of too much calcium2-4. In singular cases, hypercalcemia in this group of patients resulted from the concomitant presence of Addison’s disease5 or sarcoidosis6, from the development of primary hyperparathyroidism7; otherwise, was caused by infection with Nocardia asteroides8 or appeared during lactation9. To the best of our knowledge, although malignant tumors belong to the most common causes of hypercalcemia10, only two previous studies have reported elevated calcium levels in subjects with primary hypoparathyroidism in the course of malignancy11,12. We report here a case of a woman who developed hypercalcemia induced by metastatic lung cancer many years after having been diagnosed with primary idiopathic hypoparathyroidism.

Patient’s Presentation

At the age of 39, the patient was admitted to Hospital because of fatigue, palpitations, paresthesia and tetany, which had started six years before. The frequency of tetany episodes and the intensity of the remaining symptoms increased with time, so that at the time of admission they occurred almost daily and required intravenous calcium infusion. On physical examination, proximal muscle strength was reduced, while the deep tendon reflexes were symmetrically hypoactive. Chvostek’s and Trousseau’s signs were positive. Her family history was negative for hypocalcemia and autoimmune disorders, and there was no history of neck irradiation. A computed tomography scan of the head revealed diffuse, symmetric parenchymal calcifications involving the basal ganglia. ECG showed a prolonged QT interval. Hypocalcemia [plasma calcium levels corrected for albumin – 1.75 mmol/L (normal values: 2.2-2.6 mmol/L); ionized calcium – 0.76 mmol/L (normal values: 0.9-1.3 mmol/L)], hyperphosphatemia (1.9 mmol/L, normal values: 0.9-1.5 mmol/L), inappropriately low intact PTH levels (8 ng/L, normal values: 15-75 ng/L) and normal calcitonin levels (2 pg/mL, normal values below 10 pg/mL) proved the presence of primary idiopathic hypoparathyroidism. Oral treatment with calcitriol and calcium carbonate was initiated and resulted in a normalization of serum calcium and phosphate levels. Being treated with calcium (2 g daily) and calcitriol (1 μg daily) for the following 18 years, the pa-
tient felt well and remained largely asymptomatic. At the age of 57, she started to experience nonspecific complaints like weakness, bone pains, constipation and loss of weight. Because laboratory tests showed mild hypercalcemia (plasma calcium levels corrected for albumin – 2.7 mmol/L; ionized calcium – 1.4 mmol/L), reduced intact-PTH levels (4 ng/L) and normal 25-hydroxyvitamin D levels (56 nmol/L; reference range: 30-80 nmol/L), hypercalcemia was related to overdose of calcitriol and/or calcium carbonate and, therefore, their daily doses were reduced to 0.25 μg and 1 g, respectively. Despite changes in dosage, the patient’s condition progressively deteriorated. Besides progression in pain intensity, the patient started to complain of generalized weakness, easy fatigability, diffuse myalgia, fullness in the abdomen and headaches, which were accompanied by constantly increasing plasma calcium levels and, therefore, our patient was hospitalized. Laboratory evaluation on admission showed severe hypercalcemia (3.62 mmol/L), very low intact-PTH levels (2 pg/mL), normophosphatemia (1.3 mg/dL), normal calcitonin levels (4 pg/mL), normal plasma levels of 25-hydroxyvitamin D (52 nmol/L), as well as reduced plasma levels of calcitriol (6.5 pg/mL; reference range: 20–50 pg/mL). Moreover, laboratory tests showed anemia (hemoglobin: 7.9 g/dL) and raised erythrocyte sedimentation rate (123 mm/1st hour). A computed tomography (CT) scan of the chest revealed an enhancing mass in the right lung, the size of which was 8x10 cm, while brain and liver metastases were revealed on CT of the head and abdomen. In turn, neck ultrasound was not significant, while bone scintigraphy showed no metastatic lesions in the skeleton. Squamous-cell lung cancer was diagnosed by CT-guided biopsy of the pulmonary mass, and this neoplasm was assumed to be a disorder responsible for hypercalcemia in our patient. Plasma parathyroid hormone related peptide (PTHRP) levels measured by radioimmunoassay was found markedly elevated (18.2 pmol/L, reference range below 2 pmol/L) supporting the abnormal production of this protein by lung cancer cells. To reduce plasma calcium levels, the patient was treated with intravenous saline hydration followed by an infusion of pamidronate (60 mg) over 4 hours. The patient’s plasma calcium showed an immediate decline, reaching normal limits on day 4, while plasma PTHRP levels fell to 1.2 pmol/L within a week. Because of lung cancer, a combination chemotherapy with paclitaxel and carboplatin was given to the patient. For the first two months of chemotherapy, plasma calcium levels were maintained within the reference range and the patient did not experience clinical symptoms of hypercalcemia. Unfortunately, two months later symptomatic hypercalcemia re-appeared. Compared to the previous observation, the patient developed new brain and liver metastases, as well as previously unobserved bilateral adrenal metastases. Despite intensive treatment (fluids, furosemide, bisphosphates, calcitonin, plicamycin and glucocorticoids), during the subsequent two weeks, hypercalcemia progressed steadily reaching a value of 4.2 mmol/L (total calcium levels corrected for albumin) and 2.9 mmol/L (ionized calcium), and ended in the patient’s death.

Discussion

Only two cases of malignancy-induced hypercalcemia have been reported until now in hypoparathyroid patients. Elevated calcium levels were observed in a patient diagnosed with adult T-cell leukemia/lymphoma and in a subject with undiagnosed pancreatic carcinoma. In both these cases, as well as in the index patient hypercalcemia was accompanied by increased plasma levels of PTHRP and the production of PTHRP was probably responsible for its development. Therefore, the assessment of PTHRP can be considered as a valuable tool in the differential diagnosis of hypercalcemia in this group of patients. In our subject some accessory role in the development of elevated plasma calcium levels might be played by adrenal metastases, because their presence often results in adrenal insufficiency. Because glucocorticoids are known to reduce intestinal calcium absorption and to stimulate urine calcium excretion, subnormal glucocorticoid production may increase plasma calcium levels. Less likely is the role of metastatic bone destruction, because no bone lesions were found on scintigraphy. In turn, reduced levels of calcitriol despite normal levels of 25-hydroxyvitamin D levels argue against the association between elevated calcium levels and increased 1-α-hydroxylase activity, observed in some neoplasms and granulomatous diseases.

Patients with extremely high calcium levels secondary to parathyroid carcinoma may benefit from calcimimetics which are able to activate the extracellular calcium-sensing receptor and, as a
result to reduce PTH production\textsuperscript{10}. However, less convincing is their administration to hypercalcemic subjects with impaired parathyroid function and low PTH levels. In the index patient, a transient but short-lasting improvement was observed after treatment with intravenous pamidronate and subsequent chemotherapy. Thus our finding suggests that bisphosphates and a reduction in the tumor mass may be used in the palliative treatment of hypercalcemia in this group of patients.

Summing up, our report shows that each patient with hypoparathyroidism having increased plasma calcium levels should always be assessed for the presence of malignancy (paraneoplastic syndrome). The assessment of plasma levels of PTHRP may be helpful in the differential diagnosis of elevated calcemia in this group of patients.

References