Hypercalcemia of Malignancy in a Patient with Hypoparathyroidism: A Complicated but Treatable Condition

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Hypercalcemia in hypoparathyroidism has rarely been described. A 55-year-old male patient with primary hypoparathyroidism, left eye melanoma, and Noonan's syndrome, was referred to the endocrinology clinics due to hypoparathyroidism. Laboratories showed serum calcium of 7.8 mg/d, and phosphate 4.8 mg/dl, while using calcium carbonate 1200 mg and vitamin D3 600 IU daily. Calcitriol 0.25 mcg daily was started and calcium carbonate discontinued. Abdominopelvic CT scan and thoracolumbar MRI, showed metastasis to liver, pancreas, and osteolytic lesions in spine, humerus, and ribs. Liver biopsy confirmed metastatic melanoma. Eight weeks later, serum calcium increased to 12 mg/dl. PTH, vitamin D 1,25-OH and PTHrP levels were within the lower range of normal compatible with hypercalcemia of malignancy, secondary to osteolytic disease. Zoledronic acid was added to treat hypercalcemia and bone pain. Our case demonstrates a successful treatment and monitoring of hypocalcemia after administration of bisphosphonate in a patient with hypoparathyroidism. [*P R Health Sci J 2019;38:275-277*]

Key words: Hypercalcemia of malignancy, Hypoparathyroidism, Bisphosphonates

Hypercalcemia in a patient with primary hypoparathyroidism has rarely been described. Most of the cases reported have resulted from the treatment with excessive doses of calcium, vitamin D, or its derivatives (1).

Case Presentation

A 55-year-old male patient with primary hypoparathyroidism diagnosed when he was 12-years-old, left eye enucleation due to grade 3 uveal melanoma -epithelial cell type, and Noonan's syndrome, was referred to the endocrinology clinics due to hypoparathyroidism. During initial evaluation, the patient referred right upper quadrant abdominal pain and weight loss of 40 pounds in 9 months. Physical examination revealed an alert and oriented male, with left eye enucleation, webbed neck, and low set ears. Cardiovascular evaluation showed regular rate and rhythm, with no evidence of murmurs or gallops. Outpatient medications consisted of: calcium carbonate 1200mg + D3 600 IU po daily. Laboratories showed no electrolyte disturbances, albumin-adjusted calcium level of 7.8 mg/dl (goal of 8.0-8.5mg/dl), vitamin D of 27.9 ng/ml (nl>30ng/ml), phosphorous of 4.8 mg/dl (nl 2.5-4.3mg/dl), 24 urine calcium of 110 mg/24hrs (nl<300mg/24 hrs), with a calcium phosphate product of 35 (expected < 55mg/dl) and parathyroid hormone (PTH) of 2.9 pg/ml (15-65 pg/ml). Calcitriol 0.25 mcg po daily was started and calcium carbonate was discontinued. Due to persistent abdominal, and low back pain, chest, and abdominopelvic CT scan with IV contrast and thoracolumbar MRI were requested. Two months later during a follow up appointment, a serum albumin-adjusted calcium level of 12 mg/dl was noted, despite not been compliant with calcitriol therapy. The patient was alert and oriented and denied nausea, vomiting, constipation, anorexia, polyuria or nocturia. Imaging studies revealed metastatic lesions in pancreas and liver, and osteolytic lesions, involving thoracic and lumbar vertebrae, left humerus, and ribs. Liver biopsy confirmed metastatic melanoma. Other causes of hypercalcemia were evaluated. PTH-related peptide (PTHrp) was <0.74 pmol/L (nl<2.0 pmol/L) and 1,25-dihydroxy vitamin D was 23.9 pg/ml (nl 19-79pg/ml). Hypercalcemia of malignancy secondary to osteolytic bone lesions was diagnosed.

In view of elevated calcium levels, and bone pain, bisphosphonate therapy was considered. Although it was recognized that hypocalcemia could result with the administration of bisphosphonates and, it can be severe in

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patients with hypoparathyroidism, zoledronic acid (ZA) 4mg IV was finally given for symptomatic relief. Afterwards, serum calcium levels were cautiously monitored. Corrected serum calcium level before therapy was 12.3 mg/dl, but 48 hours after the first dose of ZA, it decreased to 7.4 mg/dl. The patient was alert, oriented and cooperative. Denied muscle cramps, numbness, tingling sensation in the perioral area, with negative Chvostek's and Trousseau's signs at physical examination. Renal function remained at baseline. Due to stable clinical picture, the patient was started on oral therapy with calcitriol 0.5 mcg po daily and calcium carbonate 500 mg two times daily. Serum corrected calcium levels were evaluated every 48 hours. At day 3, corrected calcium level was 8.3 mg/dl. Therapy with calcitriol and calcium carbonate was down titrated to calcitriol 0.5 mcg and calcium carbonate 500 mg daily on days 4 to 8, and then, to calcitriol 0.5 mcg daily, based on serum corrected calcium levels followed for 2 weeks, to reach a goal of serum albumin-adjusted calcium levels.

The patient continues receiving ZA every 28 days, along with systemic chemotherapy consisting of nivolumab. Calcium levels have remained within goal on calcitriol 0.5mcg po daily in-between bisphosphonate dosing periods. He continues with strict monitoring and management with calcitriol and calcium carbonate after every ZA dose. Bone pain has markedly improved and metastatic melanoma lesions have remained stable.

Discussion

Hypercalcemia of malignancy can be successfully treated. Paraneoplastic syndrome due to elevated PTHrp is among the most common causes, followed by bone metastasis, (20%) and ectopic parathyroid hormone production (1% of cases) (2). Other causes of hypercalcemia must be considered, including an increased production of 1,25- dihydroxy vitamin D in granulomatous diseases and, infectious processes, excessive ingestion of vitamin D and calcium supplements (3, 4).

The goal of therapy for hypercalcemia of malignancy is to achieve stable serum calcium concentration by inhibiting bone resorption and increasing urinary calcium excretion. Bisphosphonates can decrease serum calcium levels by osteoclast activity inhibition and by stimulating osteoclast apoptosis. Pamidronate has been traditionally used to treat this condition. Krysiac, R. et al, reported a case of severe hypercalcemia in a patient with hypoparathyroidism secondary to PTHrp due to squamous cell carcinoma of the lung. In this case, the patient was treated with IV pamidronate showing transient resolution of hypercalcemia (1). ZA is a new-generation bisphosphonate, now approved by the US Food and Drug Administration as a therapeutic option for hypercalcemia of malignancy. Described as more effective in reducing serum calcium levels than previously used bisphosphonates (5). Studies have shown that ZA produced a higher rate of calcium normalization, and faster onset of action than pamidronate, while maintaining safety (6). Bisphosphonates can cause hypocalcemia due to reduction of calcium efflux from bone. Most patients do not develop hypocalcemia because of compensatory mechanisms, the most important of which is an increased secretion of PTH (7). However, in patients with hypoparathyroidism treatment becomes very challenging since the lack of PTH production precludes the occurrence of this compensatory response, exposing for a higher risk of hypocalcemia.

Our unusual case highlights the importance of considering other causes of hypercalcemia in patients with hypoparathyroidism, besides treatment overreplacement. Malignancies must be thought in this population and appropriate therapy, can be successfully given. There are no specific guidelines to follow and to treat hypocalcemia developed after bisphosphonate therapy in a patient with hypoparathyroidism, but strict monitoring is necessary. Our case demonstrates a successful therapeutic approach and monitoring of hypocalcemia after administration of bisphosphonate. Another interesting fact from our case is that tumor-induced hypercalcemia secondary to melanoma is uncommon with a reported incidence of only 1.1% (8).

Few cases of hypercalcemia of malignancy have been reported in patients with hypoparathyroidism, and, to our knowledge, this is the first case secondary to osteolytic metastatic disease. The assessment of PTHrp, 1,25-dihydroxy vitamin D and imaging studies to evaluate lytic bone lesions in patients with hypoparathyroidism and hypercalcemia is imperative for the differential diagnosis. Therapy with bisphosphonates can be successfully implemented in this group of patients.

Resumen

Hipercalcemia en pacientes con hipoparatiroidismo es sumamente raro. Presentamos el caso de un paciente masculino de 55 años, con hipoparatiroidismo primario, melanoma del ojo izquierdo y síndrome de Noonan, el cual fue referido a las clínicas de endocrinología debido a su hipoparatiroidismo. Sus laboratorios mostraban un nivel de calcio corregido en 7.8 mg/dl y niveles de fosfato en 4.8 mg/dl, mientras utilizaba carbonato de calcio 1200 mg y vitamina D3 600 IU diario. Se descontinuo esta terapia y se comenzó en Calcitriol 0.25 mcg diario. Tomografía computarizada del abdomen y pelvis y un MRI toracolumbar demostraron enfermedad metastásica a hígado, páncreas y lesiones osteolíticas en las vértebras, humero y costillas. Se le realizó una biopsia de hígado, la cual confirmó metástasis de melanoma. Ocho semanas más tarde, los niveles de calcio habían aumentado a 12 mg/dl. Los niveles de PTH, vitamina D 1,25-OH y PTHrp, estaban dentro del valor normal hacia el nivel bajo, compatible con hipercalcemia de malignidad, secundario a enfermedad osteolíticas. El paciente recibió terapia con ácido zoledrónico para aliviar la hipercalcemia y el dolor oseo. Nuestro caso demuestra un tratamiento y monitoreo exitoso de hipocalcemia luego de la administración de bifosfonatos en un paciente con hipoparatiroidismo.

References

1. Krysiak R, Handzlik, G, Okopien B. Humoral Hypocalcemia of malignancy in a patient with hypoparathyroidism. Eur Rev Med Pharmacol Sci 2012;16:1127-1129.
2. Sternlicht H, and Glezerman I. Hypercalcemia of malignancy and new treatment options. Ther Clin Risk Manag 2015;11:1779–1788.
3. Jacobs T, Bilezikian J. Rare causes of Hypercalcemia. J Clin Endocrinol Metab 2005;90:6316-6322.
4. Dockrell D, Poland G. Hypercalcemia in a Patient with Hypoparathyroidism. Mayo Clin Proc 1997;72:757–760.
5. Berenson JR. Treatment of hypercalcemia of malignancy with bisphosphonates. Semin Oncol 2002;29:12-8.
6. Major P, Coleman R. Zoledronic acid in the treatment of hypercalcemia of malignancy: results of the international clinical development program. Semin Oncol 2001;2:17-24.
7. Won-Seok D, Jin-Kyung P, Myung-Il P, Hyeong-Seok K, Sung-Ho K, and Duk-Hyun L. Bisphosphonate-induced Severe Hypocalcemia - A Case Report. J Bone Metab 2012;19:139–145.
8. Grottes JM, Dumon JC, Body JJ. Hypercalcemia of melanoma: incidence, pathogenesis, and therapy with bisphosphonates. Melanoma Res 2001;11:477-482.